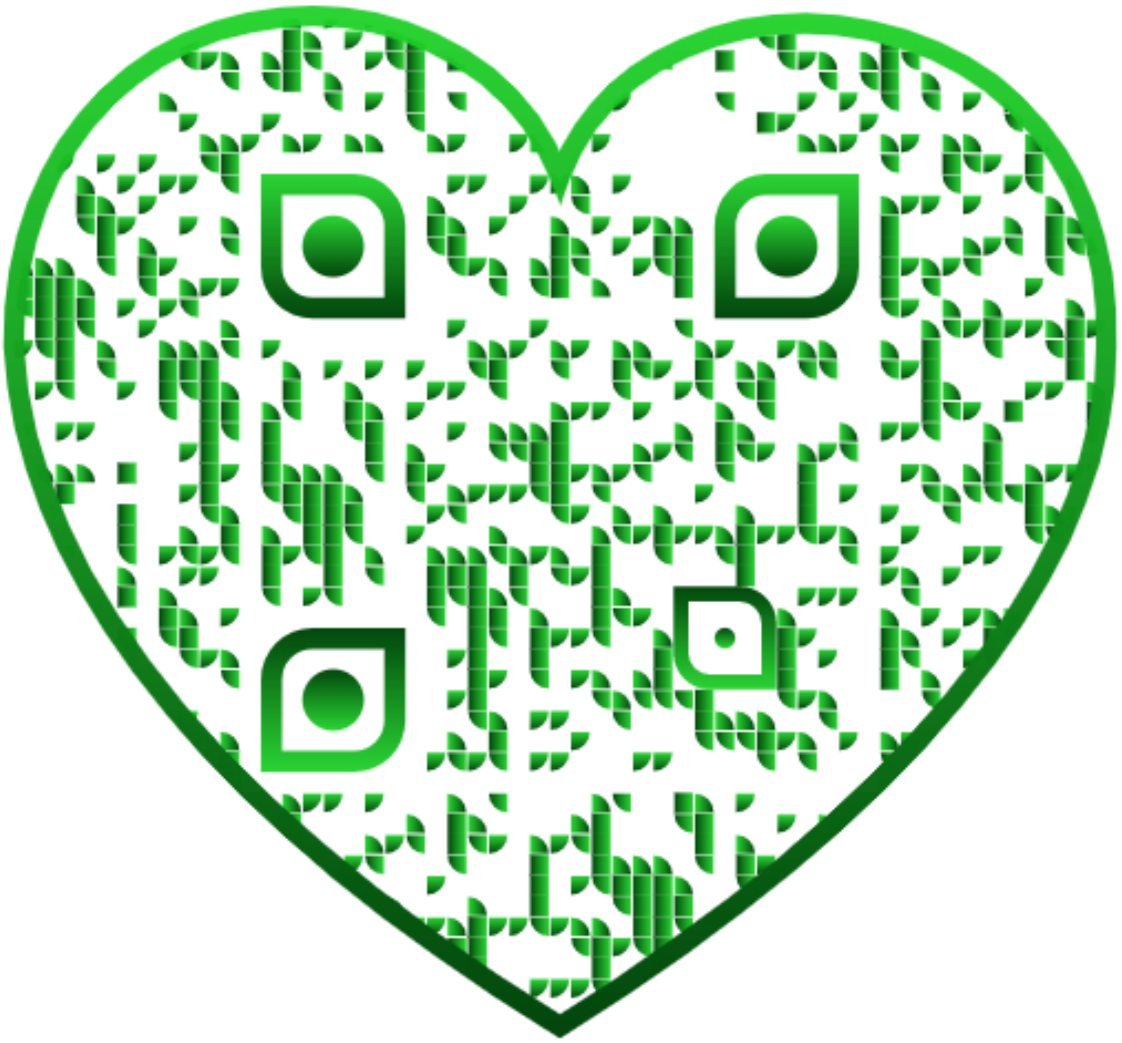
Good Manufacturing Practices (GMP) Presentation

عمل طلاب المجموعة الثانية التالية اسماءهم :.

١. رزق يوسف حسن يوسف السنة
٢. محمد خالد محمد شنان
٣. مازن حسن محمد العطافي
٤. ابراهيم انور احمد الروحاني
٥. ادريس عبدالله احمد عيدان
٦. عبدالرحمن محمد سعد سعد
٧. فتحي انيس سعيد القباطي
٨. عبدالخالق علي شارد العماري
٩. محمد عباس صالح هواش
١٠. ضياء سعد صالح هواش
١١. أسامة محمد احمد نعمان
١٢. عبد الرحمن محمد المليكي
١٣. عميد علي شرف ثابت
١٤. عبد الرقيب عبدالوهاب الصالحي
١٥. محمد طه الريامي
١٦. محمد راجح محمد معصار
١٧. محمد احمد فتحي العريقي
١٨. عبدالقادر محمد الصبري
١٩. عبدالله احمد اللقاسي
٢٠. محمد عبد الرحيم الصبري
٢١. زياد محمد غالب منصر

تحت أشراف البروفسور / محمود مهيوب البريهي



1- Pharmaceutical Industry Profile

Objecteves

- presents a broad overview of strategic industry driving forces to develop a solid informational framework for the facility professional's guidance.

- Key issues and concepts covered include speed to market, performance and conformance, cost of goods, risk management, and supply chain, as well as other issues that bear on facilities planning, design, delivery, and operation.

INTRODUCTION

- **Good Manufacturing Practices (GMP): is a system for ensuring that products are consistently produced and controlled according to quality standards.**
- **Good Manufacturing Practices (GMP)—regulatory-driven, quality control guidelines—were developed by the pharma-focused regulatory bodies that grew significantly in the 1960s.**
- **Pharma Industry Development**

Year	1900	1940	1960	1990	2000 +
Focus	Manufacturing Chemists	Prescription (Rx)	Prescription (Rx)	Rx, Over the Counter Generics	Outsource Supply Chain
Scope	Local	Local	International	Global	Global

INTRODUCTION

- A body of coordinated GMP policy is developing, providing an expanded "tool book" of guidance for facilities professionals that emphasize quality control, and forming the framework for planning and delivering modern GMP manufacturing facilities.

- **THE CURRENT SITUATION.**
- The global pharmaceutical market is growing in impact to the world's well-being and economic activity.
- Previously, the largest pharmaceutical company had only a few percent market share, typically concentrated in a few medical specialty areas.

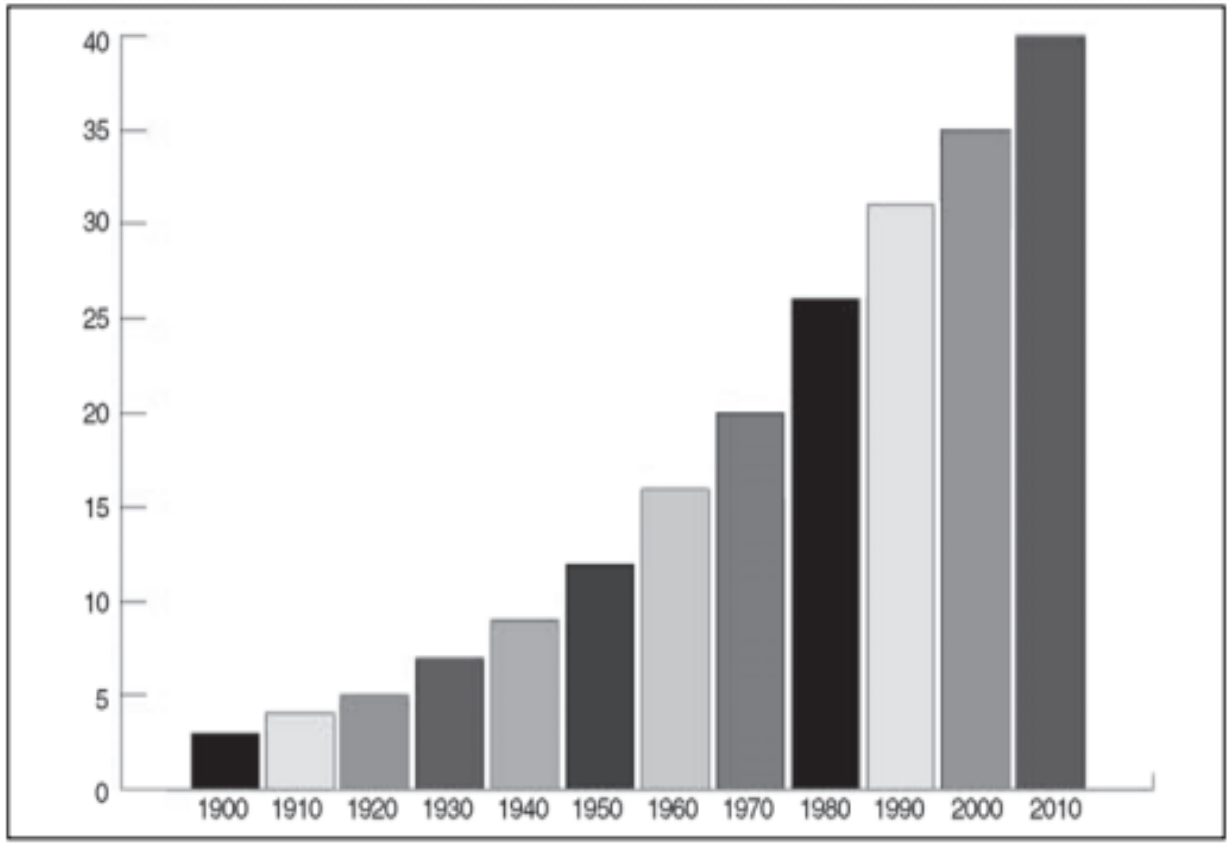
A LOOK AHEAD

- Conforming and performing to the many economic and regulatory requirements is clearly the manufacturing objective of the future.
- The future market place appears ripe for additional consolidations where firms will continue to combine in order to gain financial leverage and global marketing presence.
- Global demographics appear to strongly favor the increased use of prescription medicines to manage and/or eliminate disease.
- Future manufacturing plants will be expected to run smoothly with minimal disruptions and high confidence levels to eliminate possibilities of product recall.
- Evolving GMP are likely to spread throughout the entire "quality scheme," and will include personnel training to raise and maintain competencies of staff, consultants, and suppliers as well as mastery of technology and equipment.

STRATEGIC ISSUES: POLITICAL / SOCIAL.

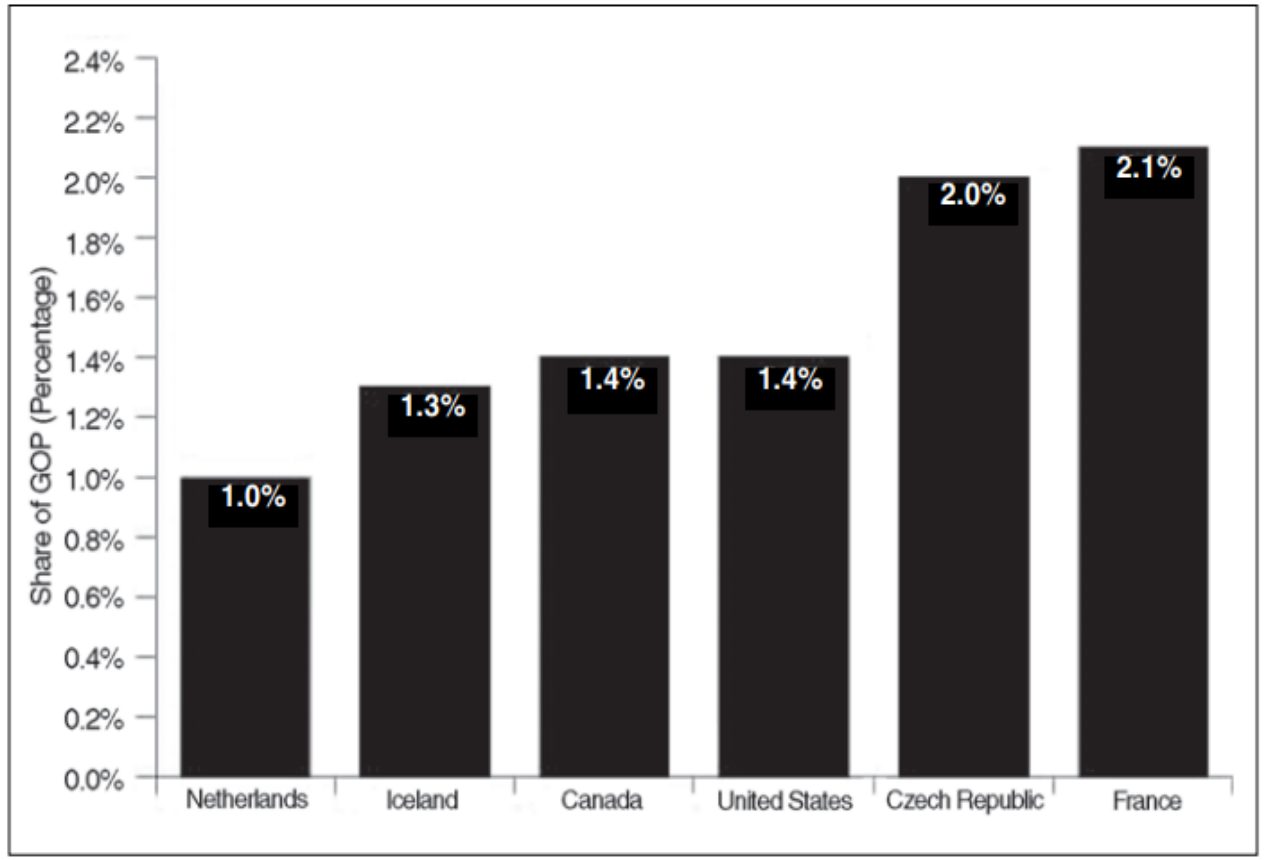
The graying of America (and the world) is a significant force in public policy.

- **Growth in Number of People Over 65 (in Millions) Every day several thousand Americans celebrate their 65th birthdays. Some 1.4 million Americans are in their nineties, and another 64,000 are 100 or older: Year 2030 estimated population —70 million.**



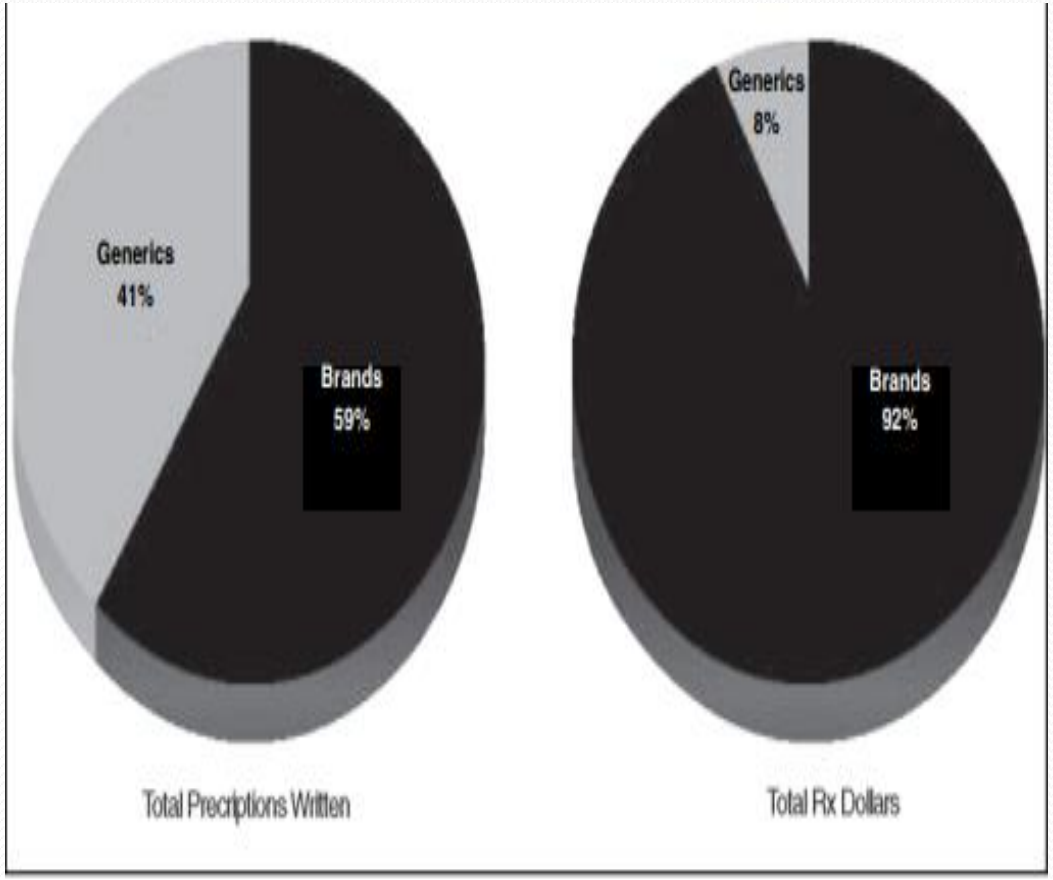
STRATEGIC ISSUES: POLITICAL / SOCIAL.

- **Pharmaceuticals' Share of Gross Domestic Product in Industrialized Countries.**



Source: CE CD, *DE CD Health Data*, CD ROM, 2002.

Market Share vs. Dollar Volume

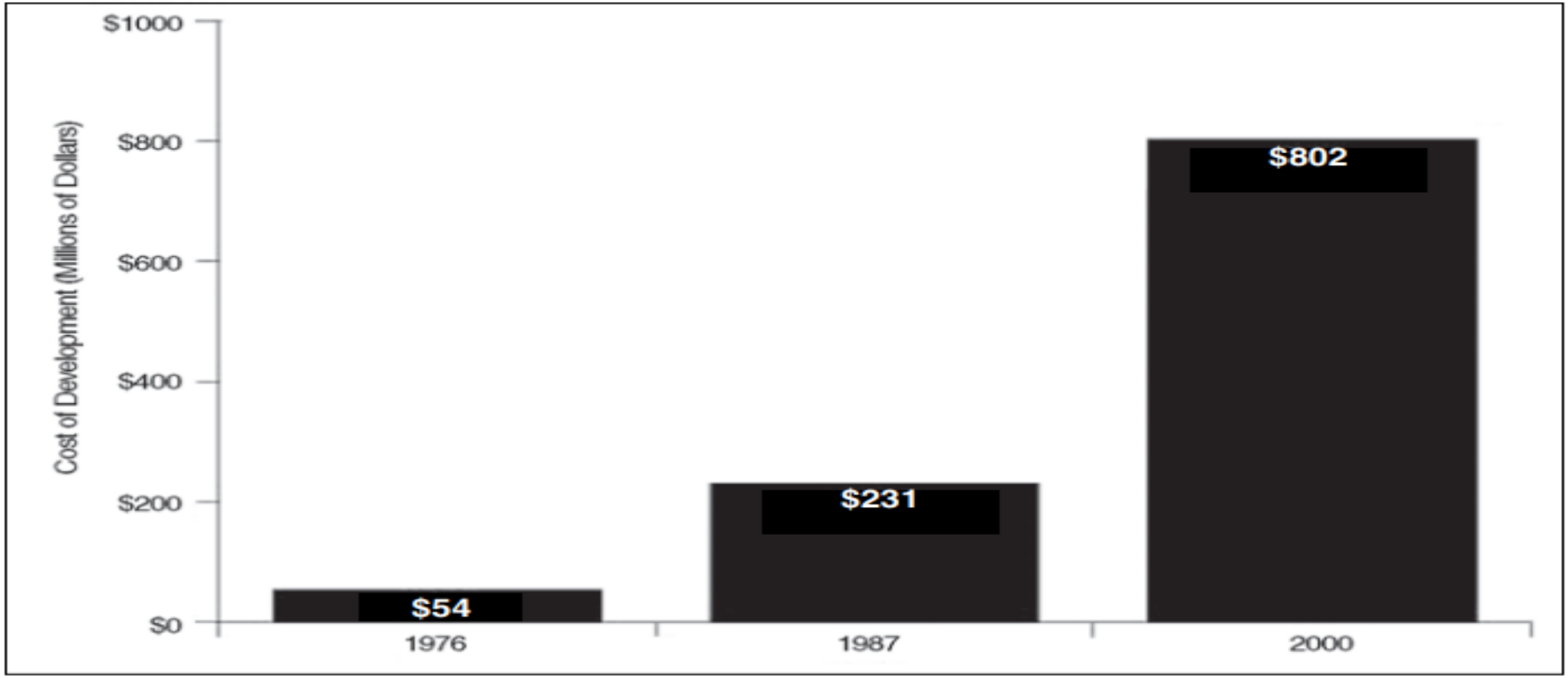


REGULATORY ISSUES

- **The pharmaceutical industry** is strongly regulated with many legal requirements to comply with global GMPs, as well as safety, health, and environmental regulations promulgated by federal, state, and local authorities.
- **The primary health care regulators (FDA, MCA, JIT, and WHO)**
- **They are** cooperating more than ever to rationalize rules and improve risks and safety profiles among a fractured supply chain market place where suppliers, contract manufacturers, **and integrated firms are producing a growing list of products delivered in varying dosage forms to a wide group of globally based consumers.**

REGULATORY ISSUES

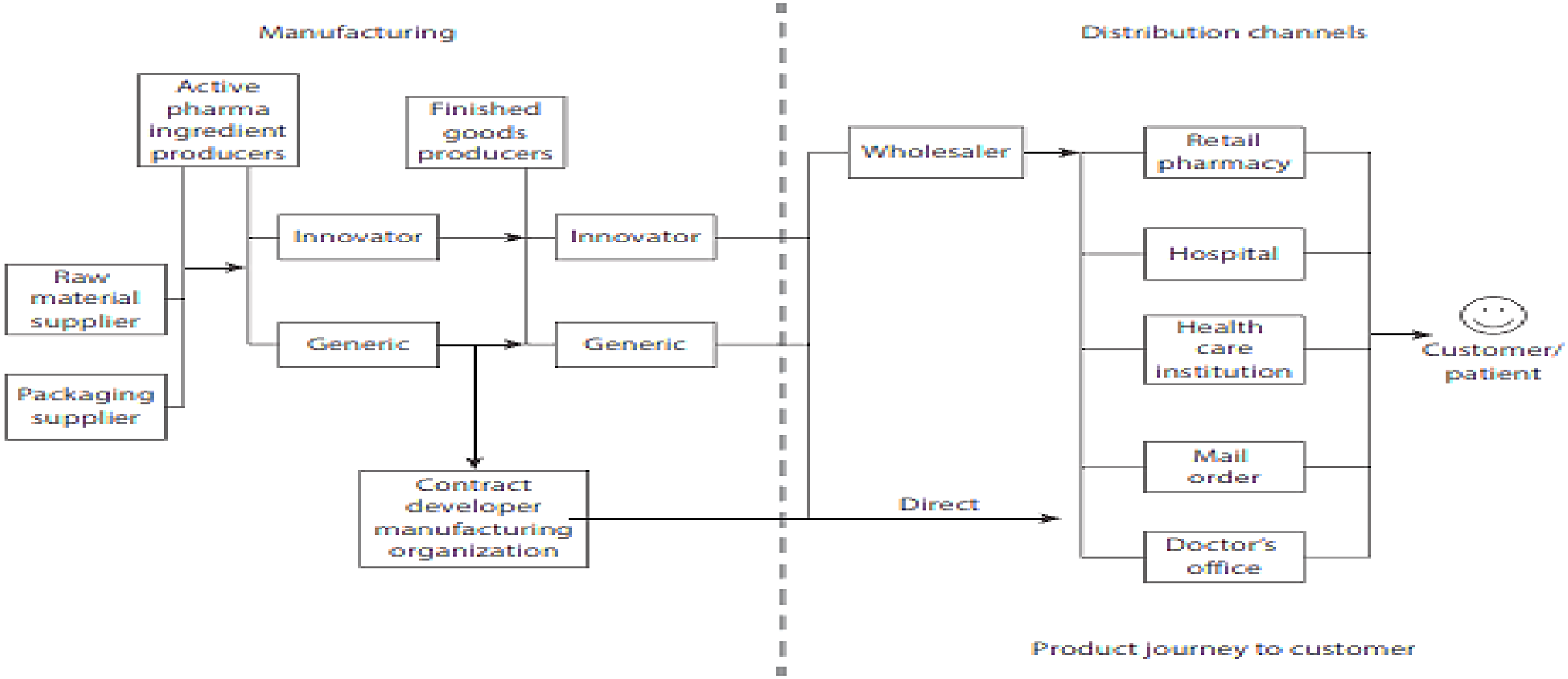
Cost of Developing a New Drug Over Time



Source: DiMasi, et al., *J. Health Ecco.* 1991 10.107–142 and Tufts Center for the Study of Drug Development, 2001.

SOURCING AND SUPPLY ISSUES

Typical Pharma Industry Facility Services Supply Chain



E 1.14 Pharmaceutical supply landscape.

MARKETING ISSUES

- The global pharmaceutical industry is driven by successful marketing and distribution.
- Successful market competition relies heavily on novel therapeutic indications and attractive economics.
- Insurers are also powerful market forces by placing limitations on price reimbursements and access.
- GDPs can assist the facility professional to design and deliver and start-up new/upgraded facilities in less time.

Expanding Markets

- From 1989 to 2001, the worldwide pharmaceutical market increased from $117.8 to $351.8 billion, representing a compound annual growth of nearly 10%. The US market grew at a compounded rate of 14.6% over the same period, increasing from roughly $33 billion to $172 billion.

LEGAL ISSUES

- The modern pharmaceutical industry operates within a highly active legal environment. Product liability actions are enormously influential on company policy and operations.

- Highly publicized regulatory-based legal actions are very costly in terms of remediation and reputation.

- Product recalls arising from GMP failures, coupled with the associated legal defense, offer considerable incentives for organizations to produce products in consistent, compliant fashion. A prudent balance of risk management and cost positioning is essential.

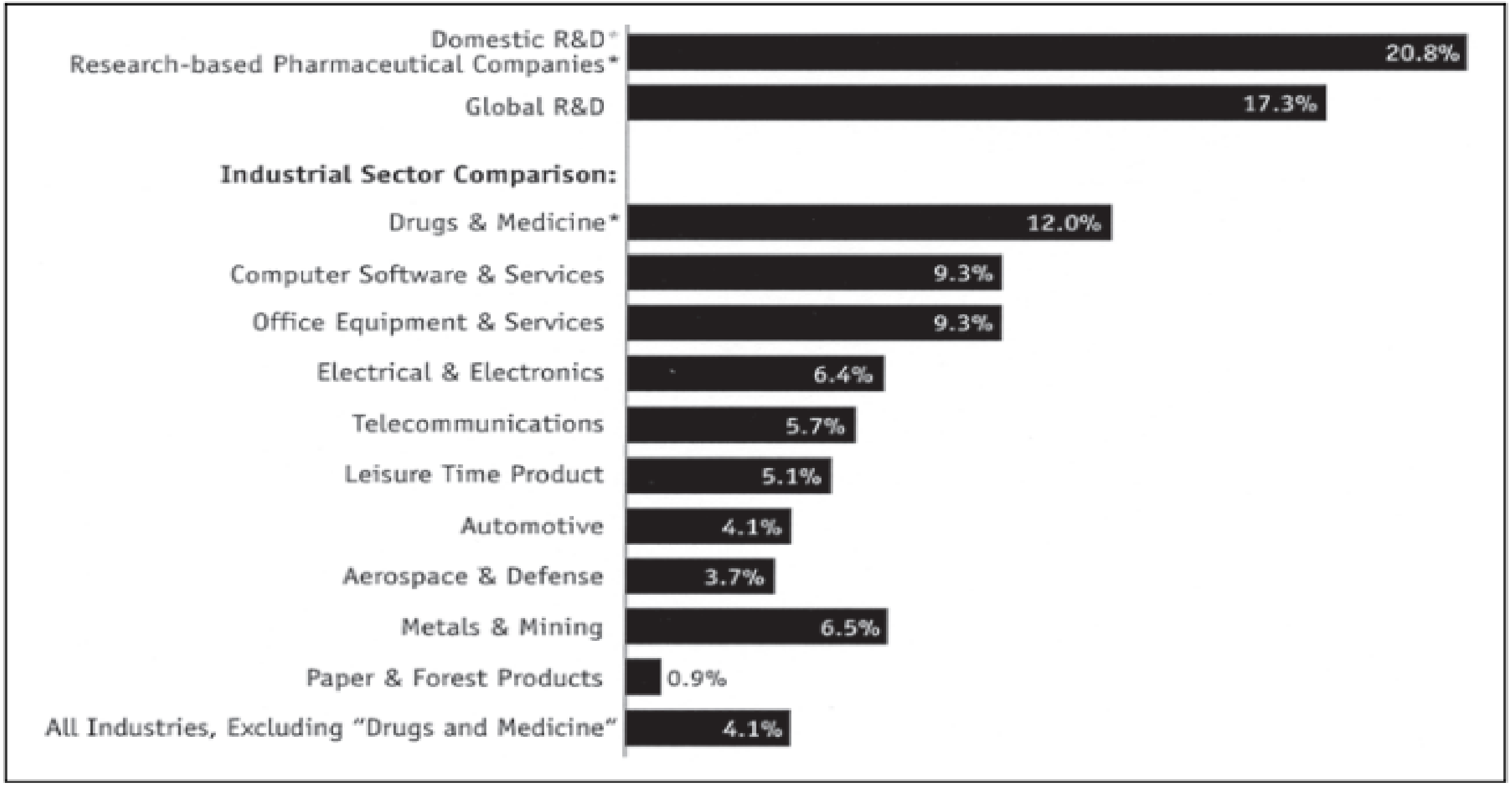
FINANCIAL ISSUES

- Pharmaceutical companies generally enjoy a solid reputation for financial stability with long-term investor yields well above average for research-intensive companies.
- The global financial environment rewards companies for well spent capital and prudent investing in R&D and marketing.
- Achieving efficiencies in capital deployment and delivering acceptable "cost of goods" is an important economic activity for the industry as competition increases and gross margins are directed toward R&D and marketing.
- Applying GDPs can help an organization obtain more leverage for their outlays through better risk management and efficient product delivery derived from excellent facilities that perform (deliver in an aligned way) and conform to evolving regulatory initiatives.

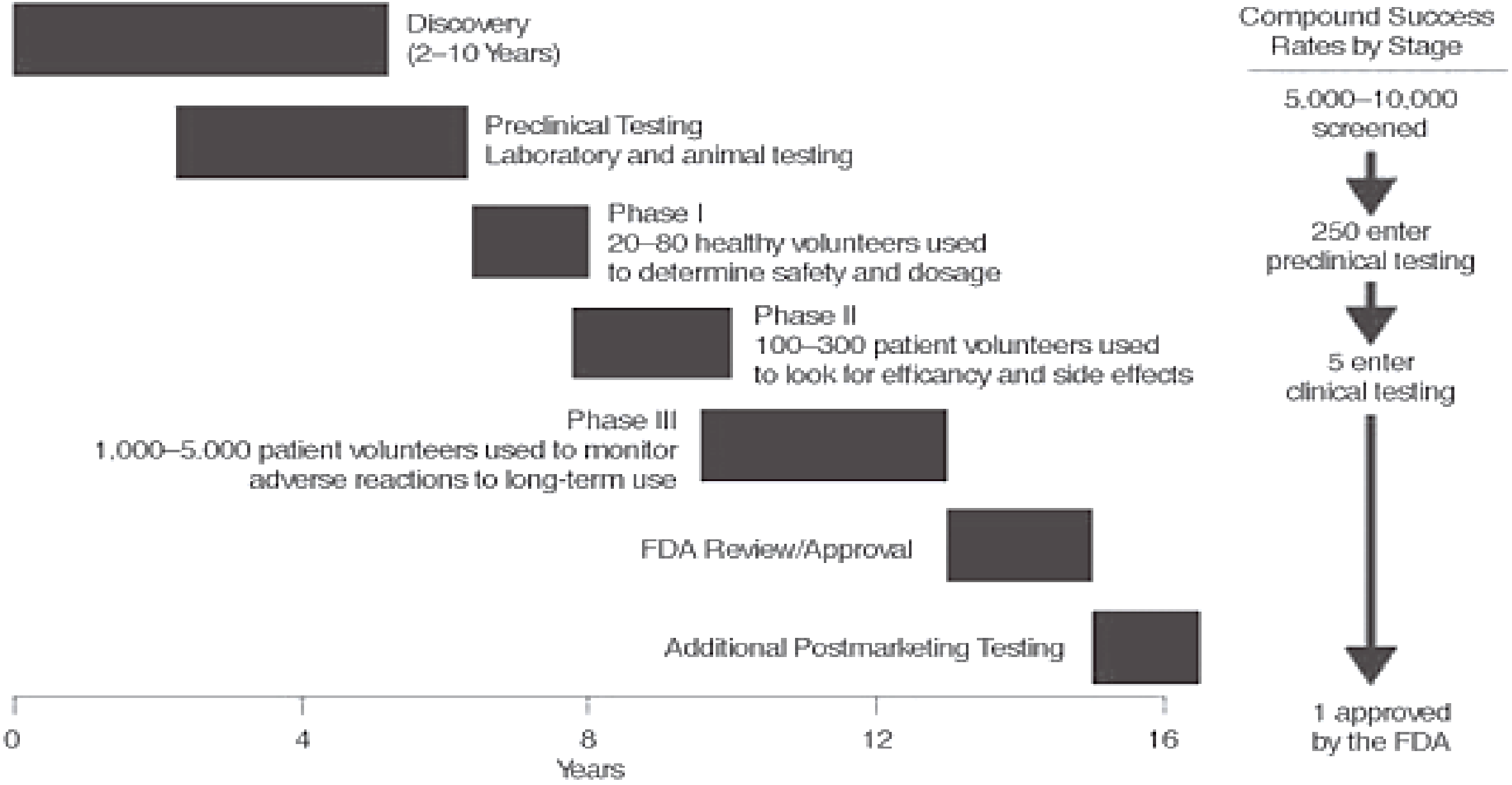
TECHNOLOGY/R&D ISSUES

- **The pharma industry depends on innovation and technology for the development and delivery of capital products and services**
- **Historically, the industry outspends virtually all others in the percentage of sales dollars invested in R&D·**
- **Technically challenging production processes demand increased efforts from well-positioned facilities and/or new alliances/partnerships to bring products to market·**

R&D as Sales Percent



Compound Success Rates by Stages



New Product Approvals Over Time

Figure 2: First-in-Class New Drug Approvals as a Percentage of Overall New Drug Approvals* by FDA, 2017–2021

First-in-class refers to new drug approvals with a new mechanism of action different from existing therapies as of the time of approval by the US Food and Drug Administration's Center for Drug Evaluation and Research.

54%	40%	42%	32%	33%
2021: 50 new drugs approved; 27 first-in-class	**2020**: 53 new drugs approved; 21 first-in-class	**2019**: 48 new drugs approved; 20 first-in-class	**2018**: 59 new drugs approved; 19 first-in-class	**2017**: 46 new drugs approved; 15 first-in-class

*New drug approvals refer to new molecular entities approved under new drug applications or as new therapeutic biologics approved under biologics license applications by the US Food and Drug Administration's Center for Drug Evaluation and Research.

Source: US Food and Drug Administration's Center for Drug Evaluation and Research

Typical Project Cycle

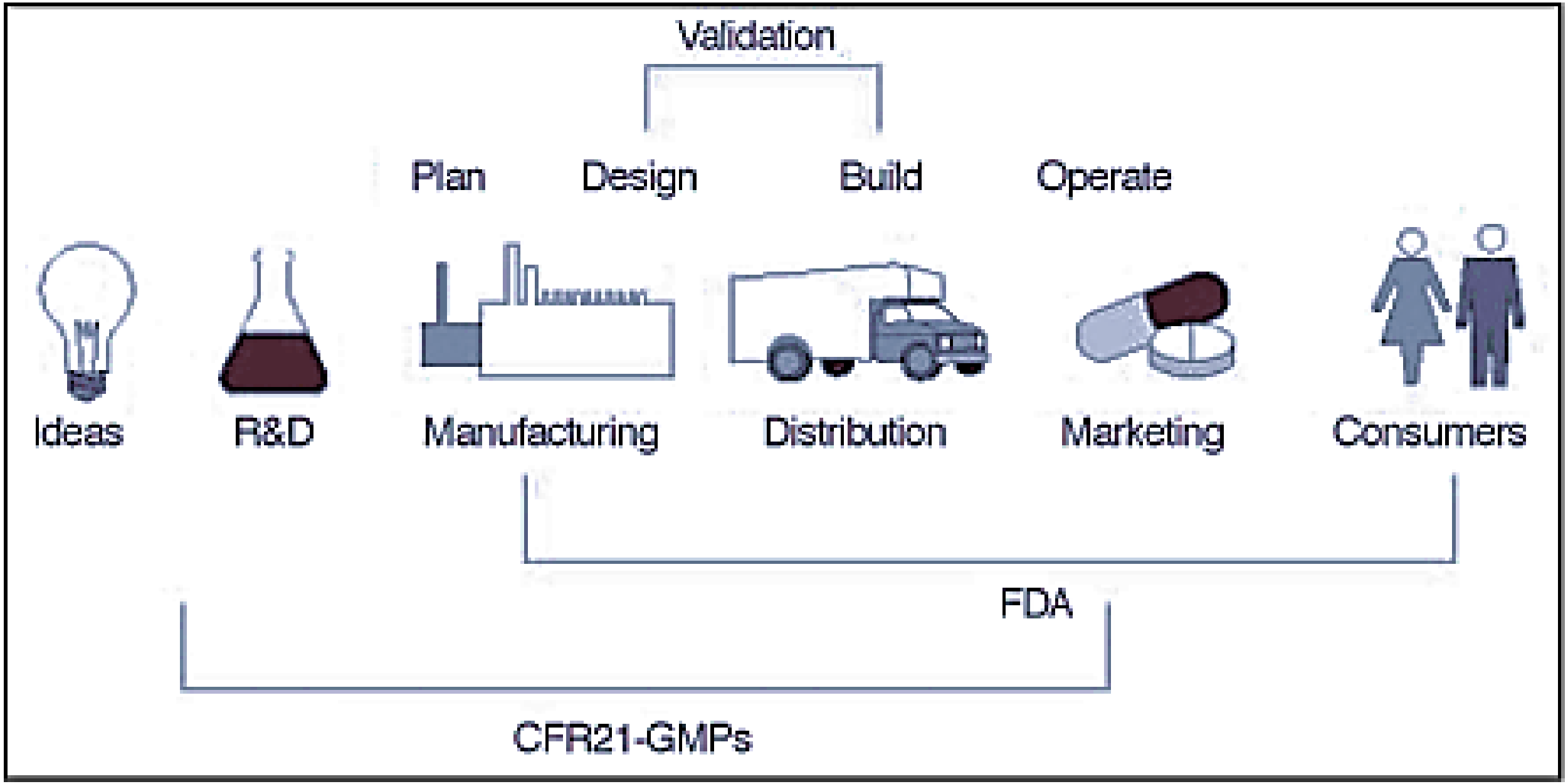


TABLE 1.7
Top 20 Global Corporation Sales: 2013

	2013 Rank	2013 Sales (US$ mn)	2013 Growth (LC$ %)	2012 Sales (US$ mn)
Global market		874,611	4.5	857,710
Novartis	1	50,576	1.9	50,521
Pfizer	2	44,330	–2.6	46,707
Sanofi	3	38,181	1.4	38,531
Merck & Co., Inc.	4	36,350	–7.0	39,891
Roche	5	36,146	5.3	34,958
GlaxoSmithKline	6	32,544	1.5	32,736
Johnson & Johnson	7	30,784	12.2	27,717
AstraZeneca Pharmaceuticals LP	8	30,257	–2.9	31,704
Teva	9	24,258	–1.8	24,762
Lilly	10	23,045	8.4	21,583
Amgen	11	18,621	8.7	17,103
AbbVie	12	18,150	2.0	17,881
Boehringer Ingelheim	13	17,375	5.7	16,889
Bayer	14	17,276	8.3	16,431
Novo Nordisk	15	14,300	15.0	12,576
Takeda	16	13,399	–9.5	15,909
Actavis	17	12,742	2.9	12,375
Mylan	18	11,087	7.4	10,325
Bristol-Myers Squibb	19	11,023	–12.9	12,756
Gilead Sciences	20	11,011	14.8	9,540

Source: IMS Health MIDAS, December 2013.

TABLE 1.8
Top 20 Global Products: 2013

Product	2013 Rank	2013 Sales (US$ mn)	2013 Growth (LC$ %)	2012 Sales (US$ mn)
Global market		874,611	4.5	857,710
Humira	1	9,851	18.5	8,318
Seretide	2	9,213	4.5	8,907
Crestor	3	8,149	1.5	8,215
Enbrel	4	7,949	8.7	7,370
Lantus	5	7,935	23.3	6,472
Nexium	6	7,863	7.0	7,407
Abilify	7	7,832	14.6	6,879
Remicade	8	7,678	7.8	7,259
Cymbalta	9	6,464	13.6	5,734
Mabthera	10	6,263	5.7	5,950
Avastin	11	5,719	8.9	5,364
Spiriva	12	5,318	7.0	4,998
Herceptin	13	5,170	3.4	5,024
Lyrica	14	5,123	14.9	4,531
Copaxone	15	4,698	5.6	4,432
Januvia	16	4,462	10.5	4,181
Lucentis	17	4,415	8.1	4,135
Neulasta	18	4,409	3.3	4,253
Glivec	19	4,136	0.9	4,149
Atripla	20	4,017	2.0	3,924

Source: IMS Health MIDAS, December 2013.

TABLE 1.9
Top 20 Global Therapy Areas: 2013

	2013 Rank	2013 Sales (US$ mn)	2013 Growth (LC$ %)	2012 Sales (US$ mn)
Global market		874,611	4.5	857,710
Oncologics	1	67,132	8.5	63,082
Pain	2	57,293	4.7	56,230
Antidiabetics	3	54,369	10.2	50,352
Antihypertensives, plain and combined	4	49,609	–1.7	52,664
Antibacterials	5	40,248	2.6	40,244
Mental health	6	39,495	–2.6	41,214
Respiratory	7	38,115	–1.8	39,357
Autoimmune diseases	8	31,080	14.4	27,473
Lipid regulators	9	28,938	–10.8	33,301
Dermatologics	10	26,778	11.3	24,815
Antiulcerants	11	25,583	1.7	26,022
Anticoagulants	12	24,076	–2.5	25,420
GI products	13	23,530	7.4	22,650
Other cardiovasculars	14	21,943	6.2	21,279
HIV antivirals	15	20,609	8.7	18,936
Nervous system disorders	16	20,170	9.7	18,758
Other central nervous system	17	18,584	6.4	17,952
Cough and cold, including flu antiviral	18	14,500	10.1	13,697
Vaccines (pure, combined, other)	19	14,076	4.5	13,851
Hematopoietic growth factors	20	13,475	5.0	12,833

Source: IMS Health MIDAS, December 2013.

Thank you

4-Architectural Design Issues

Architectural Design Issues

- **The architect is the unique integrator of the process ows, equipment, personnel ows, and mechanical systems into a building.**

Architectural Design Issues

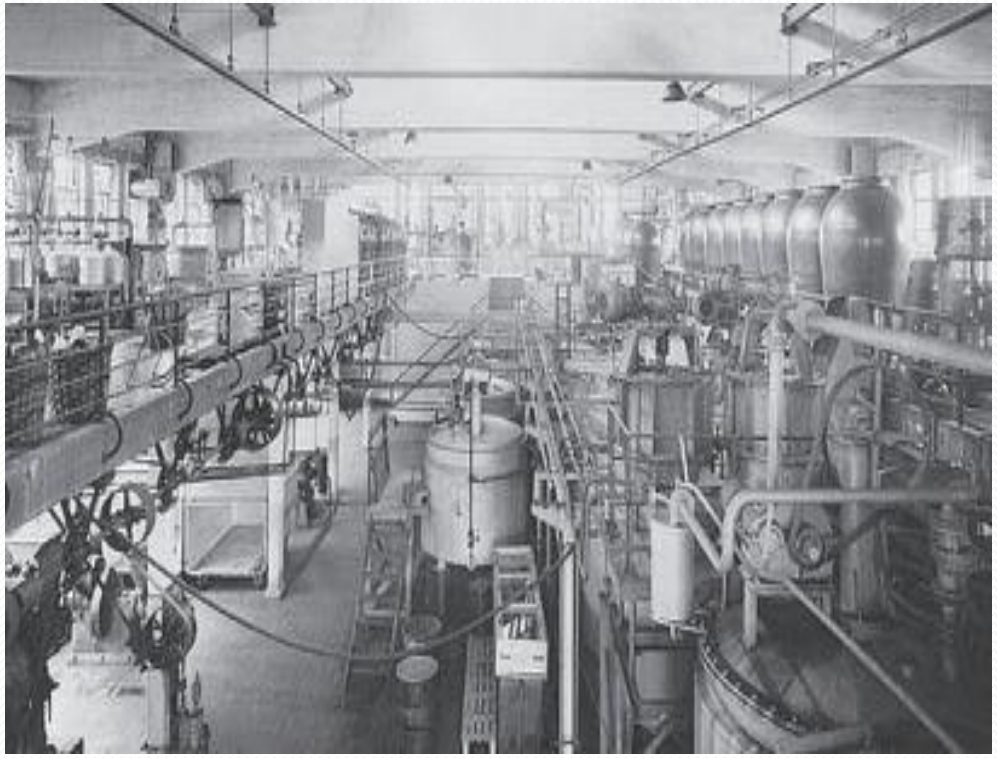
purpose of this chapter:-

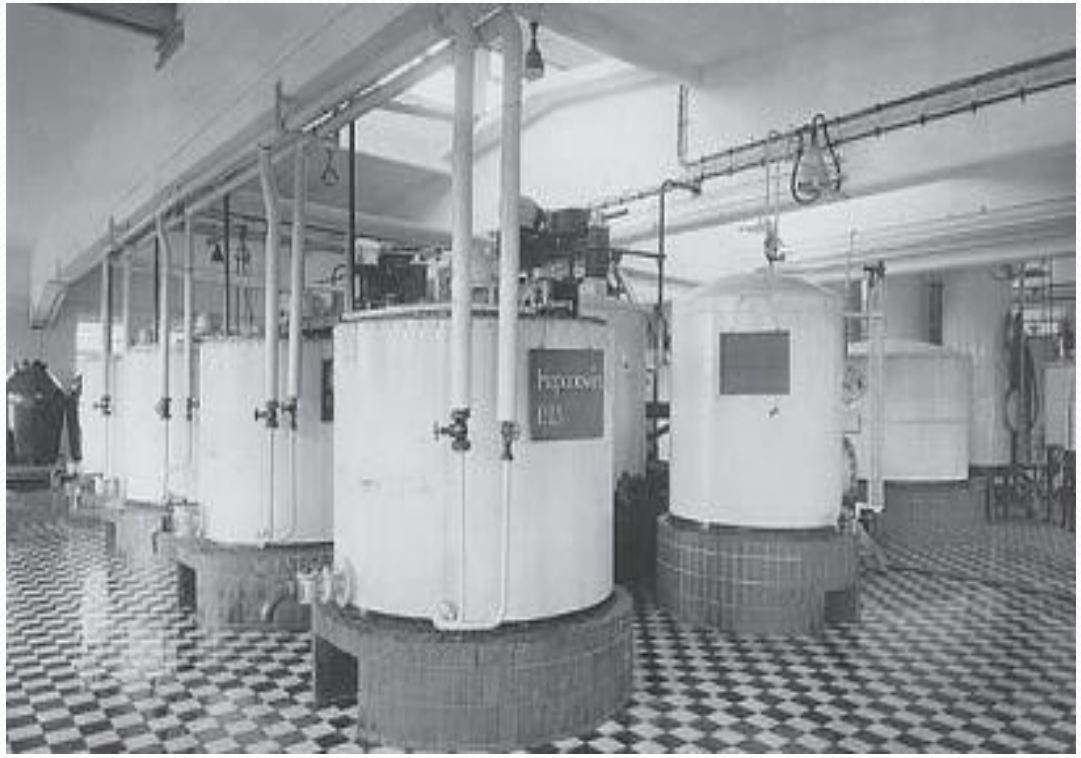
1_to assist the reader in understanding how the architectural process works and what the key architectural concepts are in.

2_incorporating current Good Manufacturing Practices (cGMPs) into the design of pharmaceutical manufacturing facilities.

Architectural Design Issues

3_building that works efciently, meets cGMPs, creates a positive workplace for the employees, and results in an efcient manufacturing facility whose output is a regulated product.





Architectural Design Issues

KEY CONCEPTS AND PRINCIPLES:-

The main types of cGMP pharmaceutical manufacturing facilities include oral solid dosage (OSD), liquid and cream,sterile,active pharmaceutical ingredient (API).

Architectural Design Issues

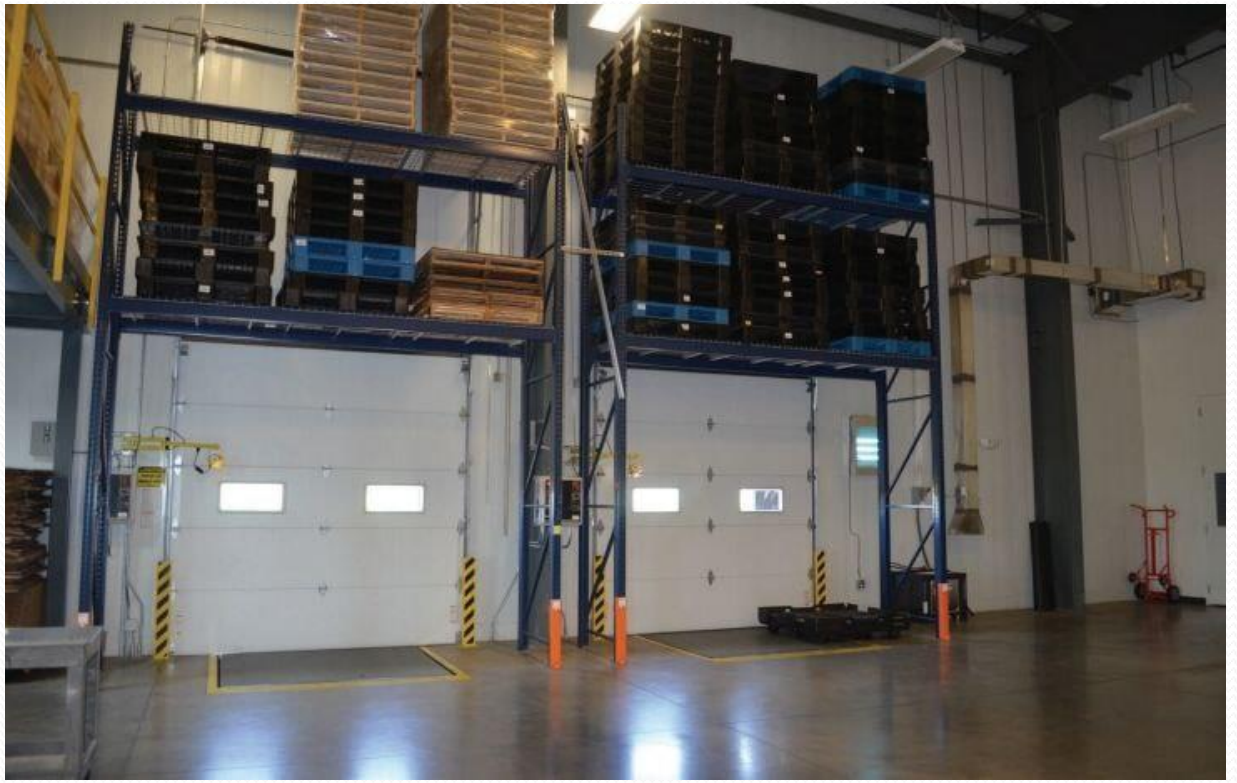
Architectural Design Issues

Architectural Design Issues

PHARMACEUTICAL MANUFACTURING AREAS:-

1-shipping and receiving areas:-

- Are Where incoming materials for the facility are received, and outgoing materials are shipped.
- These areas are generally black areas because there is no product exposure.



Architectural Design Issues

2_sample receiving and testing areas:-

is located through the shipping area doors into the warehouse area; it tests the raw materials as well as the packaging components that will be used in manufacturing.the areas where the sample is exposed for testing will be “white” areas

Architectural Design Issues

3_Weighing and Dispensing areas:-

are where the raw materials for batch or batch processing are staged for the production run.

Architectural Design Issues

Architectural Design Issues

Architectural Design Issues

4_Warehouses areas:-

are generally “black areas,” but usually have environmental contro, there may be products that require special storage conditions, such temperature and humidity control, as well as regulated products, such as narcotics

Architectural Design Issues

Architectural Design Issues

Architectural Design Issues

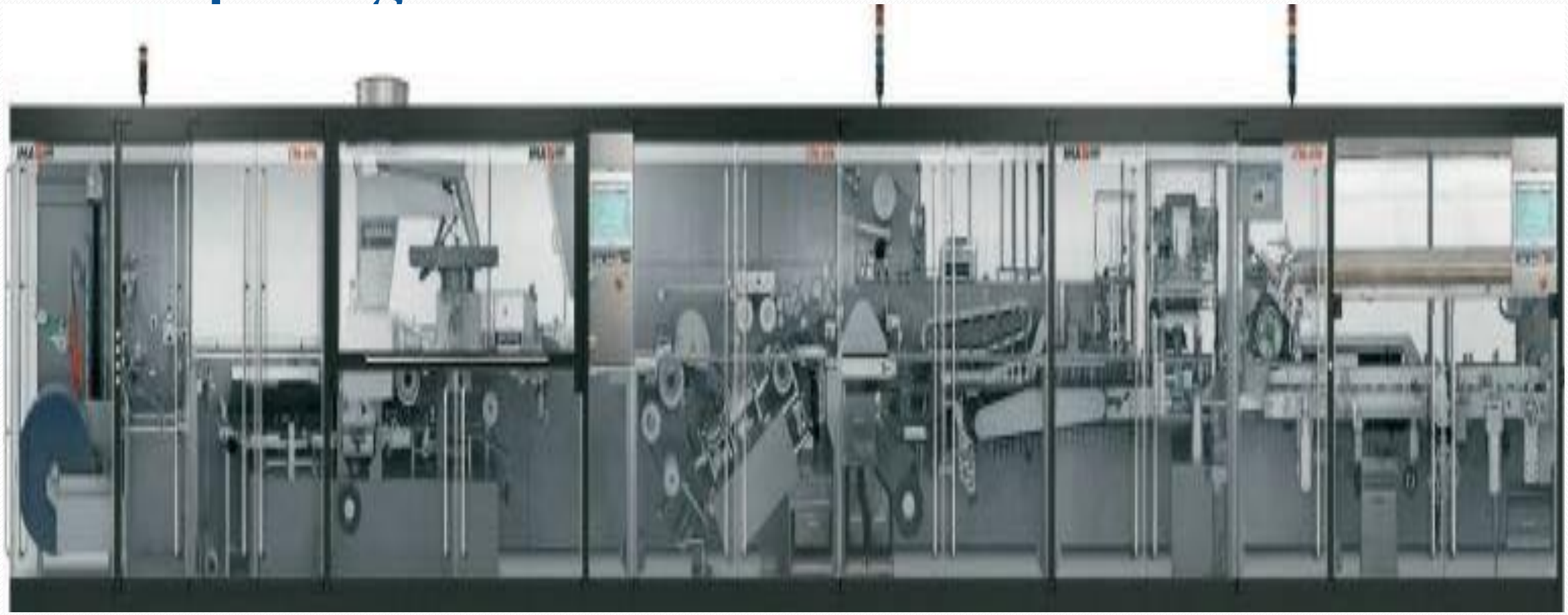
5_Manufacturing operations:-

The manufacturing room or area requirements are driven by the selection of the process equipment that is required to manufacture the product and the space needed for maintenance of the process.

Architectural Design Issues

6_Packaging operations:-

The packaging area is where the product in its nal form is packaged for distribution.



Architectural Design Issues

Quality Control Laboratory

- **The quality control laboratory should be located in a central area, easily accessible to the plant.**

Architectural Design Issues

Summary:-

- The architect designs a pharmaceutical manufacturing facility around the process, and engineering systems are required to support the process.

- Attention to detailing of utility panels, functional ows, and personnel needs creates a facility that is efcient, safe, and attractive.

Architectural Design Issues

Thank you

5- Mechanical utilities

Introduction

- Under the Food, Drug, and Cosmetic Act, a drug is deemed to be adulterated unless.
- The methods used in its manufacture, processing, packaging, holding, and the utilized Facilities and controls, conform to current Good Manufacturing Practices (cGMP).
- The product and associated manufacturing processes present design criteria that must be satisfied by the facility utility system design.

Introduction

- this chapter will cover mechanical systems design including heating, ventilating, and air conditioning (HVAC); instrumentation and control, process and piping; and fire protection systems.
- Each system must be studied to identify probable modes of failure and the reliability
- Ties and redundancies that should be provided to eliminate critical single point failure..
- Careful analysis of the failure sequence will minimize productivity loss
- And facility damage and maximize personnel safety.
- Each system should be reviewed for Maintainability, Ideally by the group that will be responsible for maintenance of That system

Commissioning and Validation

- **Commissioning, as defined in the ASHRAE Guideline 1-1996, is: The process of Ensuring that systems are designed, installed, functionally tested, and capable of Being operated and maintained to perform in conformity with the design intent.**

- **Validation is a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result that meets pre-determined acceptance criteria.**

MECHANICAL SYSTEMS

- In general, mechanical systems provide for heat transfer (both process and facility); air flow and filtration leading to maintenance of cleanliness; provision of water and
- gases for product and process requirements; and drainage and disposal of wastes.

System Design Criteria

- **Specific facility and process criteria define the system solutions that are provided.**

- **These criteria are defined as follows.**

Temperature and Moisture

- **Space and process temperature and moisture (or relative humidity) conditions are generally determined by the product or process performed.**
- **Personnel comfort is also important, though secondary to the product requirements.**

- **In general, most product or processes can be performed within temperature and relative humidity conditions comparable to human comfort and system control parameters.**

- **Continuous relative humidity levels below 15% can cause static electricity discharge.**
- **levels above 60% can be the source of microbial growth and corrosion.**

Air Cleanliness

- The level of acceptable airborne contamination within the space must be identified

- Environmental cleanliness is determined by several factors:
  - The quality of air introduced into the space
  - The quantity of air introduced into the space
  - The effectiveness of air distribution through the space
  - The effectiveness of the removal of the air contaminant.
- Removal of the contaminant as close to its source is always the most effective Method of contamination control.

Pressurization

- **Pressurization Space relative pressurization will be determined primarily by requirements of the product, but also by characteristics of the product that may adversely effect personnel.**

- **Space containment and isolation techniques, in general, can protect the product, the operator, or both.**

Building Intake and Exhaust

- **Careful attention must be paid to the incoming system air quality. This can be specific to the area in which the facility has been constructed such as an agrarian or Industrial area.**
- **An industrial area may have a more corrosive or chemical laden air quality and an agrarian area may have a higher level of seasonal air borne particulate and bio-burden.**
- **Careful consideration must be made as to the impacts of building Exhaust and relief .**

Heating Systems

- **Heating of facility and process systems is generally accomplished utilizing steam or hot water as the heat source.**

- **Steam used for sterilization of containers or equipment or that comes in direct contact with the product through a process or though humidified room air in an open product space must be “clean steam**

  .

- **Heating hot water is generally used for space heating utilized in room radiation or convection units or hot water coils in the supply air distribution system.**

Heating Systems

Heating Systems

Cooling Systems

- **Cooling of facility and process systems is generally accomplished utilizing chilled watercondenser water, or direct refrigerant expansion (DX) as the heat sink.**

- **Chilled water supply temperatures are usually in the range of 40˚–45˚F and are determined by the requirements of the cooled medium, generally air.**
- **Condenser water can also be used to cool processes besides chiller condensers.**

Central heating and cooling system control in a boiler room

Humidification Systems

- In most cases, air supplied to the space or process will require the addition of moisture to maintain relative humidity conditions.

- In the cGMP environment, the added moisture cannot be a source of contamination.

humidification Systems

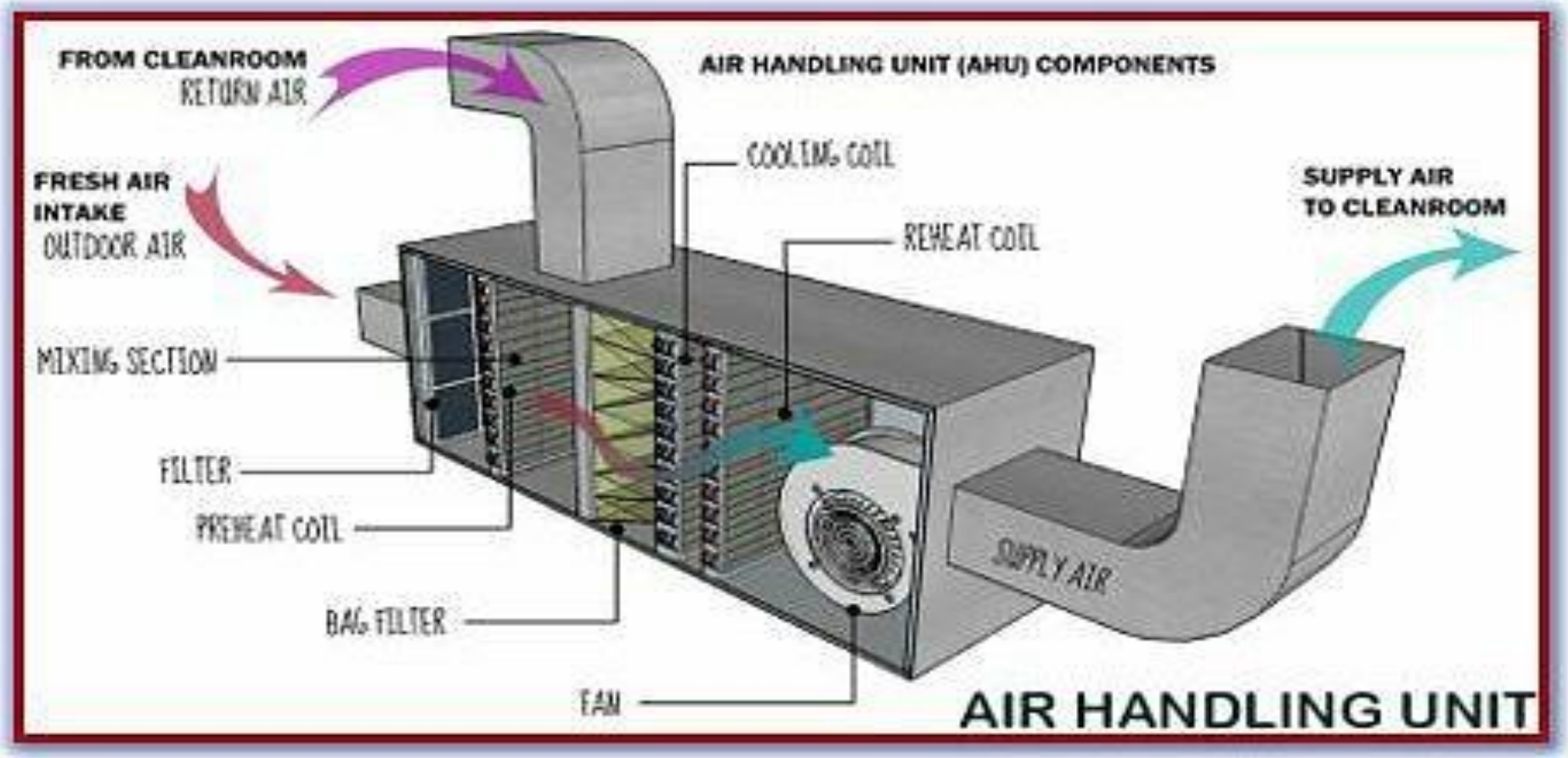
Dehumidification Systems

- **In cases of high latent loads from processes or high quantities of outside ventilation air, the building cooling system may not be capable of the higher dehumidification requirements.**

Supply Air Handling Systems

- It assists in determining the temperature, moisture level, and cleanliness of that environment. It also assists in the relative pressurization of the space or process.

Supply Air Handling Systems



Industrial ventilation system

Exhaust and Return Air Systems

- **Exhaust systems can have a great influence over the environment within the space or process that they serve.**

- **They evacuate contaminant or contaminated air to be fil-tered or processed in some other manner and returned to the supply air unit or to theat-mosphere.**

Exhaust and Return Air Systems

Dust Collection

- **Extremely high levels of particulate require larger filter surface areas and a means of collecting the particulate build-up from the filtration material.**
- **A dust collector is essentially a plenum.**

Dust Collection

PROCESS AND PIPING SYSTEMS

- **The process and piping systems disciplines, including plumbing, gases, true process systems, and fire protection, provide a critical role in the manufacture of pharmaceutical products**

Domestic Cold Water.

Domestic Cold Water.

- Two pipes with cold water flowing from the floor and a valve from the main water supply, domestic plumbing, visible copper pipes

Water Systems

Domestic Cold Water.

- **Water supplied by the local authority to the building or site is generally referred to as domestic cold water**
- **Domestic cold water is generally used for the following purposes:**

• General non-purified water usage including toilet rooms, equipment wash (not including final rinse), water fountains, etc.

• Source water for the domestic hot water system

• Source water for further purified water systems

• Makeup water for HVAC water systems

domestic heating system

Independent heat-recovery boiler with white hot water tank, domestic heating system.

Water Systems

- •Makeup water for HVAC water systems

It is permissible for potable domestic cold water to be used for cleaning and initial rinse of drug product contact surfaces, such as containers, closures, and equipment.

- Domestic Hot Water
- The domestic hot water system utilizes domestic cold water as a source.
- is heated generally by steam or electric resistance and stored for use.
- Domestic hot water is used for ordinary facility usages such as toilet rooms, equipment wash (not including final rinse), etc.

Drainage Systems

- Drainage systems remove effluent from spaces, systems, or process.
- There are Different drainage system types

1. Sanitary Waste System
2. Laboratory Waste System
3. Process Waste System
4. Hazardous Material Waste and Retention
5. Storm Drainage System

Sanitary System.

Laboratory Waste System

Gas Systems

- Many types of gases are utilized in the manufacturing process.
- The most prevalent of these include compressed air use in process and controls, breathing air for hazardous environments, nitrogen, vacuum, vacuum cleaning, natural gas, propane, and other process systems.

Gas system

Nitrogen product system

General Design Requirements

- **The building will typically be provided with one or a combination of systems to provide automatic fire suppression and protection throughout the building.**

- **In general the first choice for automatic fire suppression is a wet-pipe sprinkler system**

- **This most common type of system provides the quickest actuating, most reliable, and least expensive type of suppression for most applications.**

protection throughout the building.

- **Suppressing agents other than those mentioned above (such as CO_2, Dry Chemical, Foam and Halon alternatives) can be used to address specific hazards, and would not be used as a suppression agent throughout.**

Thank you

Good Manufacturing Practices (GMP) Presentation

عمل طلاب المجموعة الثانية التالية اسماءهم :.

١. رزق يوسف حسن يوسف السنة
٢. محمد خالد محمد شنان
٣. مازن حسن محمد العطافي
٤. ابراهيم انور احمد الروحاني
٥. ادريس عبدالله احمد عيدان
٦. عبدالرحمن محمد سعد سعد
٧. فتحي انيس سعيد القباطي
٨. عبدالخالق علي شارد العماري
٩. محمد عباس صالح هواش
١٠. ضياء سعد صالح هواش
١١. أسامة محمد احمد نعمان
١٢. زياد محمد غالب منصر
١٣. محمد عبد الرحيم الصبري
١٤. فارس احمد احمد اللقاسي
١٥. عبدالقادر محمد الصبري
١٦. احمد فتحي العريقي
١٧. محمد راجح محمد معصار
١٨. محمد طه الريامي
١٩. عبد الرقيب عبدالوهاب الصالحي
٢٠. عميد علي شرف ثابت
١٢. عبد الرحمن محمد المليكي

تحت أشراف البروفسور / محمود مهيوب البريهي

12- Biotechnology Facilities

INTRODUCTION

objectives.

- application of biotechnology facilities to produce products for the prevention and treatment of disease.
- biotechnology facility design for manufacturing biological products derived from microorganisms through fermentation or cell culture.
- basic principles and key concepts associated with current (cGMP) biomanufacturing.
- overview of bioproduction systems and bioprocess manufacturing operations.
- discusses the unique challenges to the design and delivery of biotech facilities.

prevention of process contamination

- **Biopharmaceutical manufacturing requires attention to the level of bioburden control that is appropriate for each step in the process.**
- **system of quality risk management (QRM), which ensures that the safety, identity, potency, purity, and quality of the drug substance are not compromised.**
- **Clean rooms, isolators, and closed process systems are employed to provide an appropriate level of protection from environmental contamination.**
- **Contamination control is fundamentally different from containment control (as may be required for a biohazard or potent compound) .it is the difference between protecting the product from the environment and protecting the environment from the product.**

prevention of process contamination

TABLE 12.1

Contaminants That Must Be Considered in Biotechnology Facility Design

Source of Contamination	Potential Risk	Facility Design Impact
Materials	Viruses, bacteria, and cross-contamination	Flow of materials, controlled raw material sampling and storage areas, quality control labs, and storage of samples, product, and waste
Manpower	Bacteria/particulate contamination and cross-contamination	Flow of personnel, gowning, and locker facilities
Equipment and environment	Bacteria and cross-contamination	Flow of product and waste, single use, closed systems, cleaning validation, utility design, air handling and room classifications, segregation of activities, and cleanable surfaces

Definitions

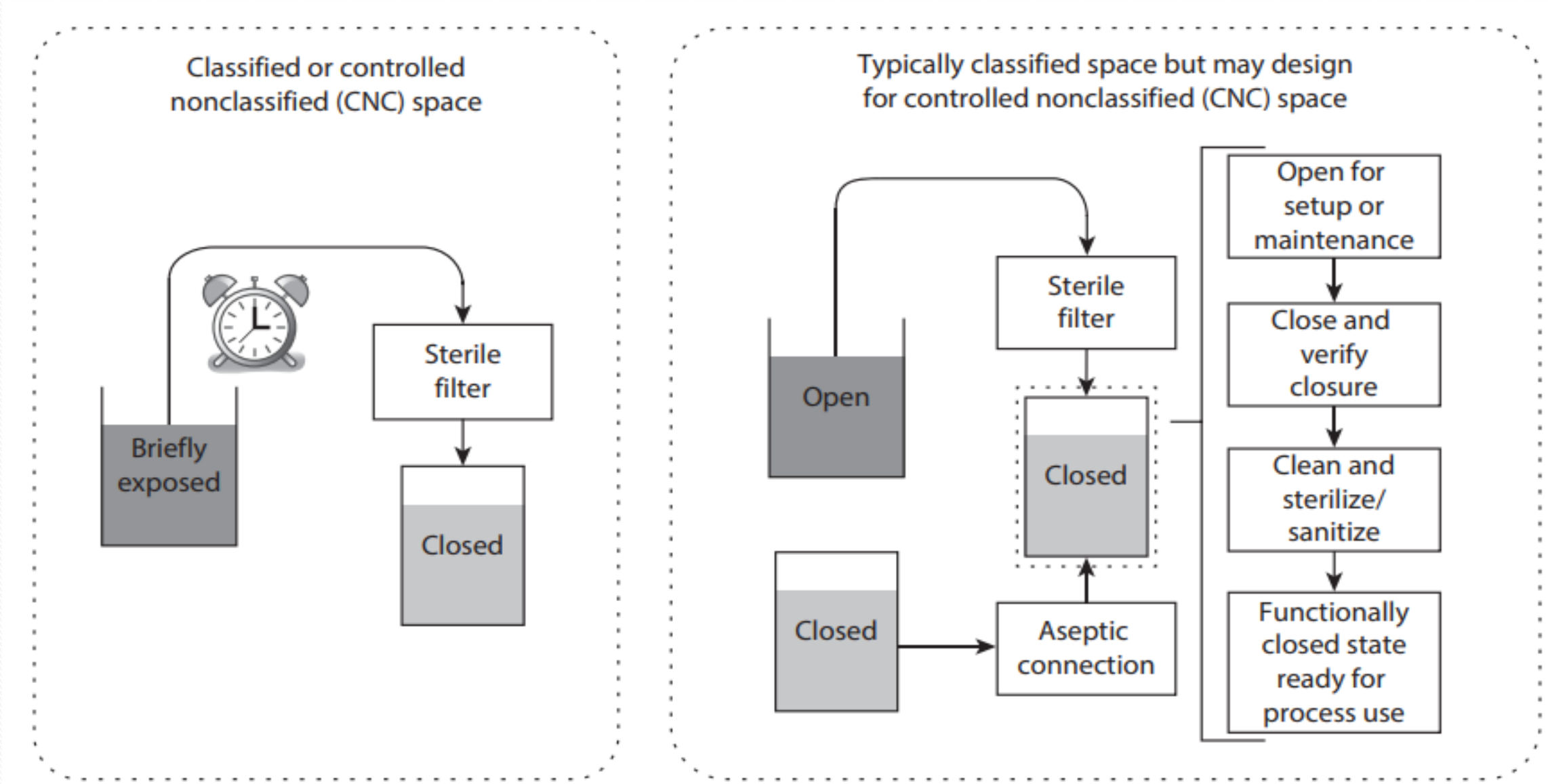
- An understanding of the contamination control terminology used to describe bioprocessing operations is critical to identify the design requirements for a biotechnology facility.
- Sterilization: refers to a condition where the probability of remaining bioburden (i.e., number of viable contaminating microorganisms present) is statistically insignificant.
- Aseptic: The most accurate term for describing bioburden-free operations in biotechnology facilities.
- Axenic: refers to a culture that contains a single strain of living organism (as intended in a bioreactor) but is entirely free of all other contaminating organisms.
- hygienic, as used in the biopharmaceutical industry, refers specically to the maintenance of cleanliness so that the product does not adversely affect human health.

prevention of process contamination

- **One determining factor in the assessment of risk in biomanufacturing is the nature of process isolation from the environment.**

- **A closed system is denfied as a "process system that is designed and operated such that the product is never exposed to the surrounding environment" .**

Briefly exposed and functionally closed processing.



BIOTECHNOLOGY FACILITY DESIGN

- **A proper approach for biotechnology facility design starts with a thorough understanding of the manufacturing process (i.e., the process flow, the timing of operations, and the equipment and utilities that are required).**

- **From this foundation, designers can proceed with architectural programming, including adjacencies and transitioning to cGMP areas, to lay out the facility.**

Production Systems

- The user requirements for biotechnology facilities are heavily influenced by the type of product (e.g., protein therapeutics, mAbs, vaccines, gene therapy, or stem cells), the propagation system (i.e., host microorganism used to produce product), and the final dosage form.
- Most biopharmaceutical products are delivered as a parenteral (i.e., injectable) dosage form, whereby the drug is injected directly into the bloodstream ·
- Biopharmaceutical products are diverse and are produced by a variety of methods. E.g. by microbial or cell culture propagation .
- The choice of propagation system has a significant impact on the manufacturing process, which, in turn, affects the equipment requirements, process utilities, area classification, flows, and space planning for the facility.

Production Systems

- **Bioburden is a particular issue with injectable drugs for the following three key reasons:**

I. **Endotoxins created by Gram-negative microbial contaminates can elicit an immune response with unwanted side effects .**

II. **Exotoxins from environmental bacteria, which are not routinely monitored, can cause cell culture death and are highly toxic to humans in small quantities.**

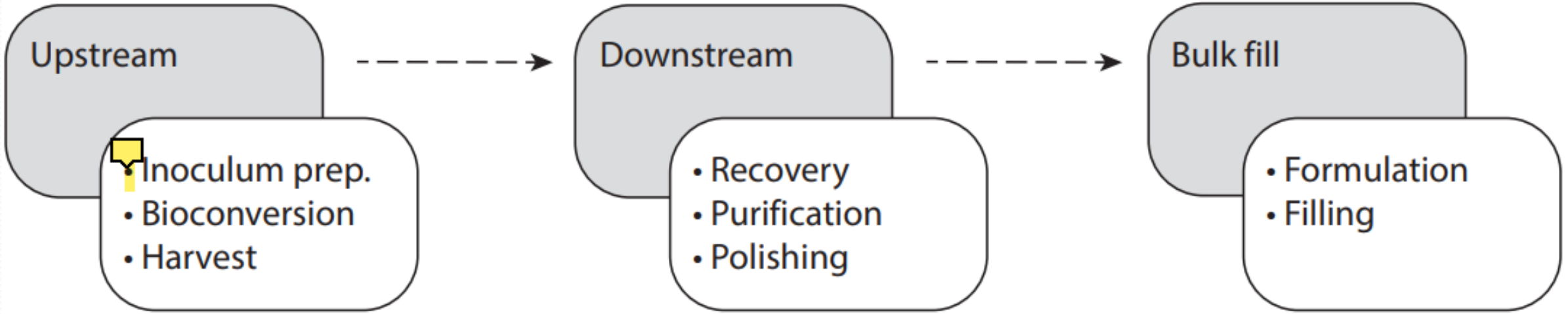
III. **Bacterial action on the product may cause unwanted variants by clipping protein chains or changing the glycosylation pattern (neither of which may be readily detectable by analytical testing).**

Bioprocess Manufacturing Operations

- In comparison with other chemical process industries, unit operations for biologics manufacturing are typically executed on a relatively small scale ·
- after the introduction of recombinant DNA technology, biopharmaceutical manufacturers became increasingly reliant on product portfolios that include drugs for small patient populations (requiring small volumes of product per batch).
- The industry typically relied on existing batch technology to provide a safe and reliable process.
- Bioprocess development for future facilities is expected to make greater use of continuous processing to enable more efficient manufacturing on a small scale.
- bioprocessing is a wet operation requiring frequent cleaning, cGMP bioprocess equipment is typically designed and constructed in a manner that facilitates external cleaning and sanitization.

Bioprocess Manufacturing Operations

- **Biotechnology manufacturing operations are typically categorized as upstream or downstream processes.**
- **Upstream, downstream, and bulk filling processes are all supported by ancillary manufacturing activities, including weigh and dispense, media preparation, buffer preparation, sterilization, and part washing operations.**

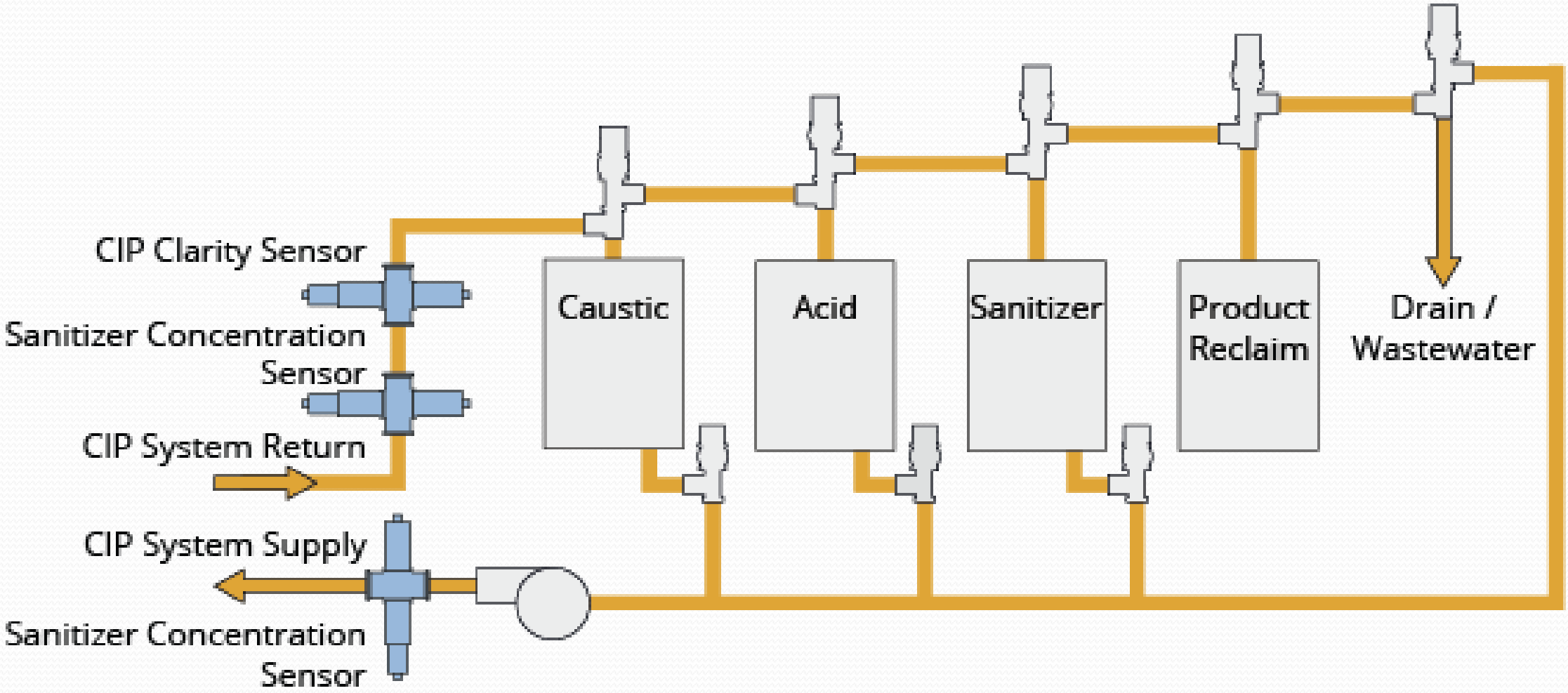


E 12.6 Typical biotechnology manufacturing operations.

Equipment Cleaning And Bioburden Control

- Traditional biomanufacturing in stainless steel equipment requires facility infrastructure for cleaning and sterilization.
- Centralized clean-in-place (CIP) systems are designed to prepare and distribute cleaning solutions throughout the plant to facilitate cleaning of equipment in situ.
- The design of distribution loops for CIP is critical because it requires piping that is correctly sloped and free of dead legs (i.e., pockets with stagnant areas).
- CIP systems can be a source of cross contamination, separate systems are typically used for buffer or media preparation and upstream and downstream operations.
- SIP and CIP stations may be required to make temporary connections to mobile tanks or process systems for equipment sanitization, sterilization, or cleaning.

Equipment Cleaning And Bioburden Control



Equipment Cleaning And Bioburden Control

Typical central CIP system. (Courtesy of Sani-Matic, Inc., Madison, WI.)

Equipment Cleaning And Bioburden Control

single-use technology

- Single-use technology may be used for biomanufacturing in which materials in contact with the process are discarded after processing.
- This technology uses gamma-irradiated bags, connectors , and tubing to enable aseptic closed processing without CIP or SIP requirements
- If single-use technology is deployed extensively in a facility, a significant reduction or elimination of CIP or SIP infrastructure requirements may be possible.
- SUS technology also provides the advantages of faster turnaround times for process systems (increasing throughput), a reduction in compendial water and waste neutralization requirements, and greater process flexibility for multiproduct manufacturing.
- Single-use solutions are commercially available for almost every step in biomanufacturing (excluding only unit operations that require pressure or temperature extremes or handling of organic solvents).

product transfer

- The method of material transfer in a bioprocess facility has a large impact on its design.
- In production-scale facilities with hard-piped product transfer, a large network of highly automated process piping, requiring SIP and CIP, is needed.
- This may require a complex system of transfer panels and automated valve clusters for routing and isolation of process uids.
- Facilities that rely heavily on single-use technology may eliminate much of the process piping infrastructure in a facility, but instead bring a relatively larger impact on loading docks, storage, and material transfer areas of the facility ·

process automation

- At the unit operation level, most process automation applications for batch processes are not complex.

- Automated system reliability and the integrity of data captured for the batch record are of paramount importance for cGMP manufacturing. This requires an automation development process that is highly structured, well documented, and validatable.

- process analytical technology (PAT) is recommended by regulatory authorities to provide "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring nal product quality"

process automation

- The next level up from basic process automation of unit operations is supervisory control and data acquisition (SCADA). The SCADA system provides a method to access equipment status, ongoing operations, and process variables for the entire manufacturing process.

- Human–machine interface (HMI) stations may be provided within clean manufacturing space to allow operators SCADA access to view and control local operations, as well as critical utilities and processes in other manufacturing areas.

- Single-use systems require far less plant automation because the cleaning and sterilization of product contact services are essentially outsourced to the SUS vendor.

- Process automation is a key enabler of continuous bioprocessing in regulated biotechnology facilities. Continuous processing in a cGMP manufacturing environment requires continuous monitoring and PAT, which enable parametric release ·

- Essentially, PAT provides continuous assurance that a process is working correctly and that the product is of the right quality throughout the process

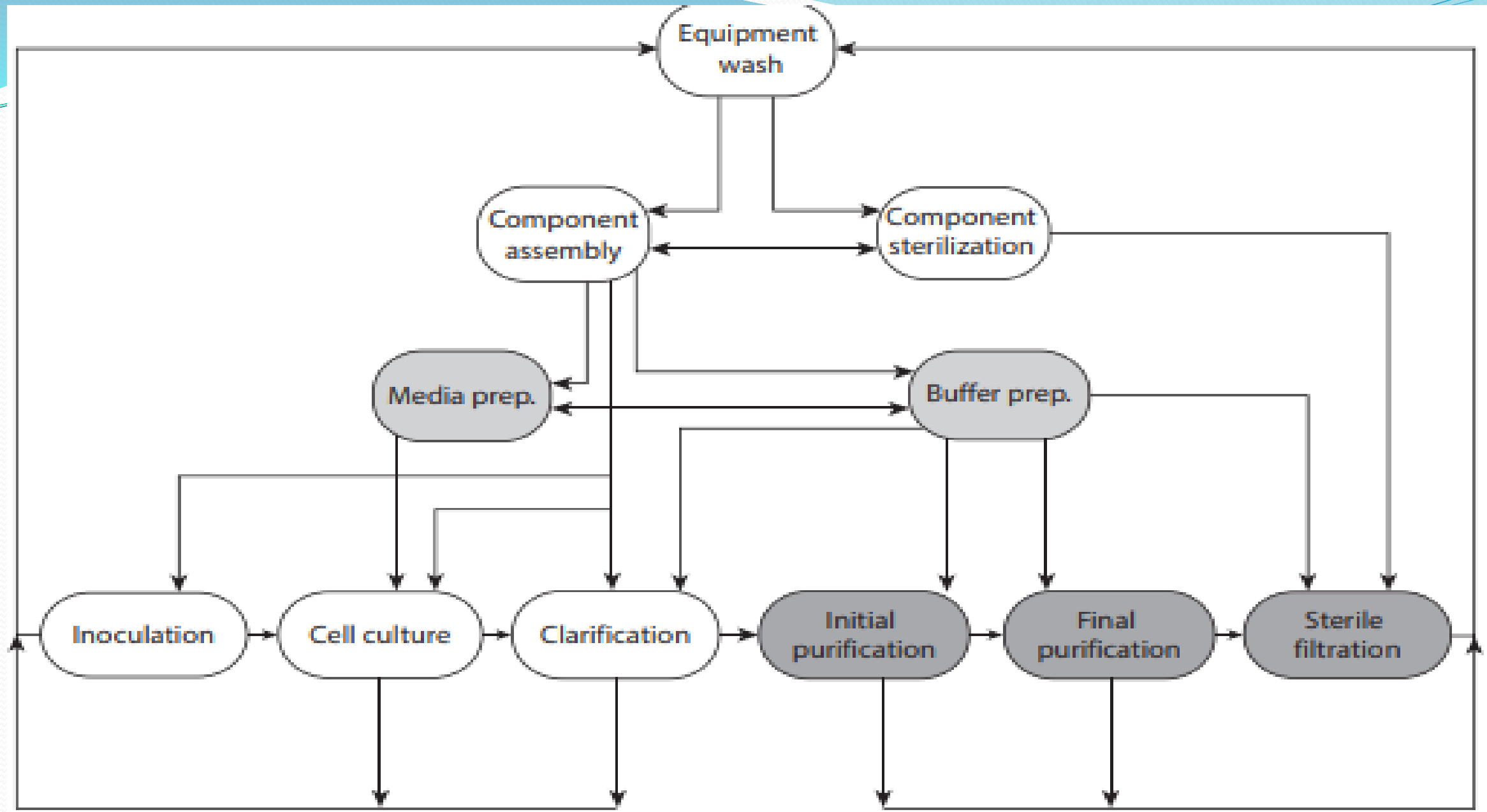
process utilities

- **The process utilities used in a biotechnology facility include general plant utilities, such as plant steam, chilled water, and compressed air, as well as clean utilities, such as compendial water, clean steam, and clean gas systems. The QRM method requires a criticality assessment of process utilities as part of facility design to identify the impact of utility systems on product quality.**

- **The reliability of process utility systems in cGMP biotechnology facilities can be every bit as critical as that of the process equipment for unit operations.**

- **As cGMP biotechnology facilities typically produce parenteral products, the clean utility systems the product must be designed to operate free of contaminates that could be carried into the product stream.**

- **Unless the process is small enough to be supported by outsourced compendial water supplies, a utility system is typically required to generate, store, and distribute water for injection (WFI) for process formulation and for equipment and parts' nal rinse during cleaning.**



E 12.15 Overview of typical area adjacencies for biotechnology manufacturing.

Biomanufacturing area requirements

TABLE 12.2

Biomanufacturing Area Requirements

Operational Area	Description	Adjacencies and User Requirements
Media preparation	Area where media (cell food) for the growth of cells is mixed and formulated.	Adjacencies: upstream processing. May require dust collection for open operations.
Buffer preparation	Area where buffer solutions are mixed, formulated, and staged for the purification process.	Adjacencies: downstream processing. May require dust collection for open operations.
Inoculum preparation	Provides benchtop equipment, BSC, freezer, and incubators to grow cells from a small frozen vial to a volume sufficient to inoculate a bioreactor.	Adjacencies: upstream processing. Typically classified space with ISO 5 BSC and ISO 7 background for axenic open process operations.
Upstream processing (cell culture and fermentation)	Area where cell material is grown to a targeted volume and concentration (titer). This area contains a seed train of progressively large-sized bioreactors plus full-scale production bioreactors.	Adjacencies: media preparation, inoculum preparation, cell separation. Typically ISO 8 or CNC space with process utilities supporting bioreactors.
Cell separation	Area where cellular material is separated from product. Frequently combined in same room as upstream processing. This area contains harvest equipment and clarified product-hold vessel.	Adjacencies: upstream processing, downstream processing. Segregated space with sound attenuation may be required for homogenization or centrifugation.
Downstream processing	Area where harvested material from cell separation is processed; involves multiple process steps for clarification, recovery, purification, and polishing operations (e.g., filtration, chromatography).	Adjacencies: cell separation, final purification, buffer preparation. Typically flexible classified space. May require segregated area for virus removal/inactivation before final purification.
Final purification	Area where final material is purified and transferred into bulk containers. Last step in drug substance manufacturing.	Adjacencies: downstream processing. May require classified space with ISO 5 BSC and ISO 7 background for aseptic open process operations.

TABLE 12.3
Manufacturing Support Area Requirements

Operational Area	Description	Adjacencies and User Requirements
Locker rooms	Area where personnel change from street clothes into low-lint scrubs to mitigate clean room contamination from operations staff.	Adjacencies: access and return corridors; close to manufacturing areas but not inside classified space. Typically, men's and women's locker rooms are provided with toilet and shower facilities.
Cleaning supply	A janitor's closet where cleaning and disinfectant supplies are kept.	Adjacencies: near area exit. Typically provided with potable water supply.
Returned equipment	Area where equipment used in manufacturing is returned for cleaning and sanitization.	Adjacencies: equipment preparation (and part washer), close to manufacturing areas.
Equipment preparation	Area where parts are unloaded from a part washer and typically assembled or placed in a clean bag in preparation for autoclaving.	Adjacencies: returned equipment, equipment staging. A local protection area is usually provided to keep parts free of particulates.
Equipment staging	Temporary storage area for equipment that has been autoclaved and staged until ready for reuse in manufacturing.	Adjacencies: equipment preparation. A local protection area is usually provided to prevent particulate contamination of parts as they cool down after autoclaving.
Column packing	Area where chromatography columns are prepared by transferring resin into a vertical pressure container (column).	Adjacencies: downstream processing. Typically classified space. May not be required if prepacked columns are used.
Cold room	Area for storage of processing intermediates. Occasionally purification steps may need to be executed in a cold environment.	Adjacencies: close to manufacturing. Typical environment validated for 2°C–8°C.
Freezer room	Area for dedicated product freezers.	Adjacencies: close to manufacturing.

(Continued)

TABLE 12.3 *(Continued)*
Manufacturing Support Area Requirements

Operational Area	Description	Adjacencies and User Requirements
Cell banking	Areas for master cell bank and working cell banks.	Adjacencies: none. Typically alarmed storage freezers, backup power supply.
Warehouse	Area for storage of raw material, intermediates, final products, and consumables.	Adjacencies: loading dock. Unclassified space with temperature, humidity, and access controls. Contains raw material receiving and sampling areas and segregated quarantined and released materials.
Weigh/dispense	Area for dispensing measured raw materials for manufacturing; often assembled in single-use kits for protection from contamination.	Adjacencies: warehouse. May require local protection area and dust collection for open operations.
QC laboratory	Area for processing samples for chemical/physical assays and microbiological assays (including EM and validation samples).	Adjacencies: none. Requires sample receiving and cold storage space. Typically contains segregated chemistry lab (with fume hoods) and microbiological lab (with BSC and incubators), both supported by autoclave, glass washer, purified water, and laboratory gases.
Document control	An administrative area for storage, review, and approval of new and executed QA documents.	Adjacencies: none. A secure and fireproof space for storage of master documents is required.
Maintenance and metrology	Areas for storage of spare parts, tools, and instruments, as well as bench calibration and repair activities.	Adjacencies: none.
Analytical support	Area for in-process testing by production staff.	Adjacencies: close to manufacturing.
Personnel support	Area for operations staff to gather for breaks, meetings, and computer access.	Adjacencies: none. Nonclassified space outside the gowned area.

Note: EM, environmental monitoring; QC, quality control; QA, quality assurance.

facility space programming

- Programming is a systematic process for decision making about organization and project values, goals, and requirements.
- This is the process whereby required facility spaces are idented, and the size and relationships between these spaces are established.
- In cGMP biotechnology facilities, the manufacturing and regulatory requirements should always drive the space program.
- The manufacturing process must be developed and documented at production scale with a process ow diagram (PFD) and mass balance.
- This approach should consider both the risk of product contamination and safety risks from hazardous materials ·

Process Segregation

- **Process segregation within biopharmaceutical facilities may include**

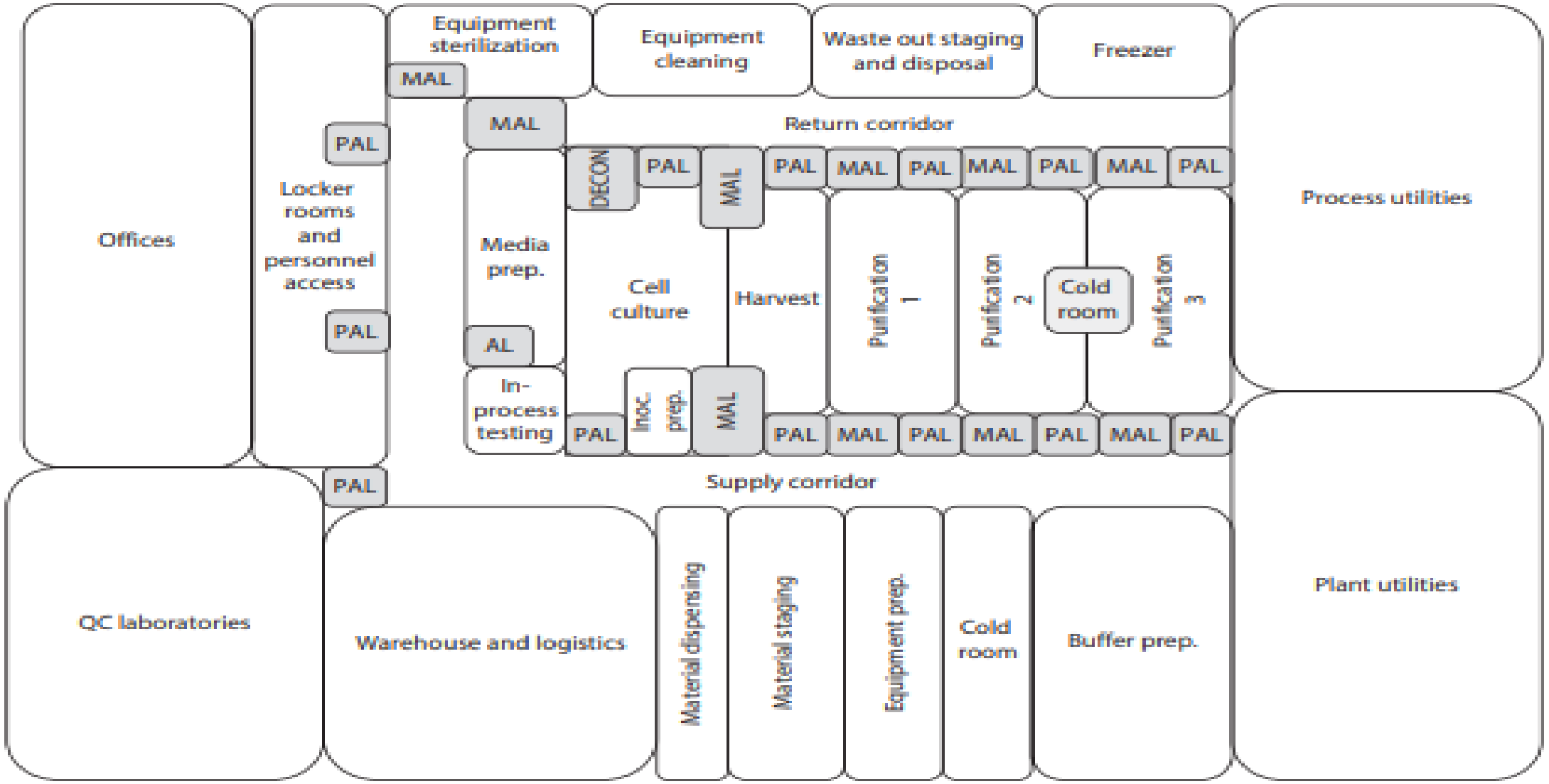
  - **Segregation from environment**
  - **Segregation from personnel**
  - **Segregation by product**
  - **Segregation by batch**
  - **Segregation of concurrent operations**
  - **Segregation of operations containing viable microorganisms**
  - **Segregation between unit operations before and after virus removal or inactivation steps.**

Area Adjacencies

- **Physical segregation in biotechnology facilities is typically developed using bubble diagrams to identify the discrete spaces required and their relationship to each other.**

- **These developmental Physical segregation in biotechnology facilities is typically developed using bubble diagrams to identify the discrete spaces required and their relationship to each other.**

- **This is a critical stage in the design development of the facility because it has a direct impact on process contamination control and regulatory compliance.**



JRE 12.16 Traditional biotech facility diagram that illustrates process segregation, relying on facility or environmental clean room classifications to protect the product.

Thank you

13- API FACILITIES

Contents

- Introduction
- Key Concepts
- Design of API Facilities
- Design Implications in Terms of Performance and Compliance
- Project Management Issues
- Trends and Future Developments

INTRODUCTION

Introduction

- Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product.
- These chemicals or biochemicals are used to produce final dosage form pharmaceutical products.
- regulated by the Food and Drug Administration (FDA) and requires adherence to current Good Manufacturing Practices (cGMPs).

Introduction

- There are many different of types of API facilities. The makeup of an API facility will depend on each of the following:

1) The type of API product;

2) The manufacturing process associated with the API product;

3) The type and configurations of the process equipment;

4) The unit operations required to synthesize, purify, dry, and size the API product;

5) The required API quality attributes and other

Introduction

Regulatory Background :

The design of an API facility must not contribute to any potential contamination of the API.

manufacturing of APIs must be in conformance with “Current Good Manufacturing Practices”

Designing API facilities from a cGMP standpoint is that pharmaceutical facilities, processing systems, and packaging equipment must be protective of the drugs manufactured, packaged, labeled, held, or distributed within them.

KEY CONCEPTS

Key Concepts

- *API Starting Material:* A raw material, intermediate, or an API that is used in the production of an API.
- *Intermediate:* "A material produced during steps of the processing of an API that undergoes further molecular change.
- *Bulk Pharmaceutical Chemical (BPC):* An older term that encompassed all chemicals.
- *Integrated Design:* An approach to plant or process design that ensures that all of the API process.
- *Integrated Project Implementation:* An approach to project implementation that ensures that all capital project activities.
- *Excipients/Inactives: are those non-API chemicals that are used in the dosage form's formulation.*

KEY CONCEPTS

- *Good Engineering Practices:* A general term used to denote commonly accepted practices for designing, installing, and commissioning equipment and systems, and the documentation associated with these project activities.

- *Good Manufacturing Practices (GMPs):* A set of rules and guidances that set forth an appropriate system for managing the quality of materials produced.

- *Process Train:* A term used to denote a collection of equipment employed in the manufacture of a stage or process step for an API or Intermediate.

- *Flexibility:* A term used to denote the versatility and interconnectability required in API facilities that produce multiple products in multiple process trains.

DESIGN OF API FACILITIES

DESIGN OF API FACILITIES

- *Types of API Production :* determine what types of operations will be performed.

- *Chemical Synthesis and Purification :* Chemical synthesis is the creation of a new molecule or chemical entity by means of a series of controlled chemical reactions.

purification steps such as filtering or centrifuging, drying, milling and particle sizing, and final packaging into bulk containers.

- *Biological Manufacturing :* chemical synthesis may be created by the fermentation of microorganisms.

DESIGN OF API FACILITIES CONT....

- *R&D, Development, and Clinical Materials :* R&D of new APIs often includes a suite of early development laboratories in which small scale processing takes place.

The development work done in these facilities should include the identification of applications for the use of Process Analytical Technology (PAT).

- *Large Scale R&D Production :* Productionthe same scale as commerciatypical base units for API production.

- *Sterile API Facilities :* are manufactured under aseptic conditions.

DESIGN OF API FACILITIES CONT....

BASIC UNIT OPERATIONS

- Raw Material Preparation, Material Transfer, and Charging Steps.
- A Reaction Step or Steps.
- A Crystallization Operation.
- Purification Operation.
- A Drying Step.
- A Drying Step.
- Equipment Cleaning.

DESIGN OF API FACILITIES CONT....

EQUIPMENT REQUIREMENTS

- Solids Preparation, Weighing, Transfer, and Charging System Components. handling system components that receive, pre-package, pre-weigh, and charge raw materials into API manufacturing processes.

- Reactor. This is the process vessel in which chemical reactions take place.

- Crystallizer: The process vessel in which crystallizations take place.

- Filter/Centrifuge: This equipment is used to separate solid materials from mother liquors or waste.

DESIGN OF API FACILITIES CONT....

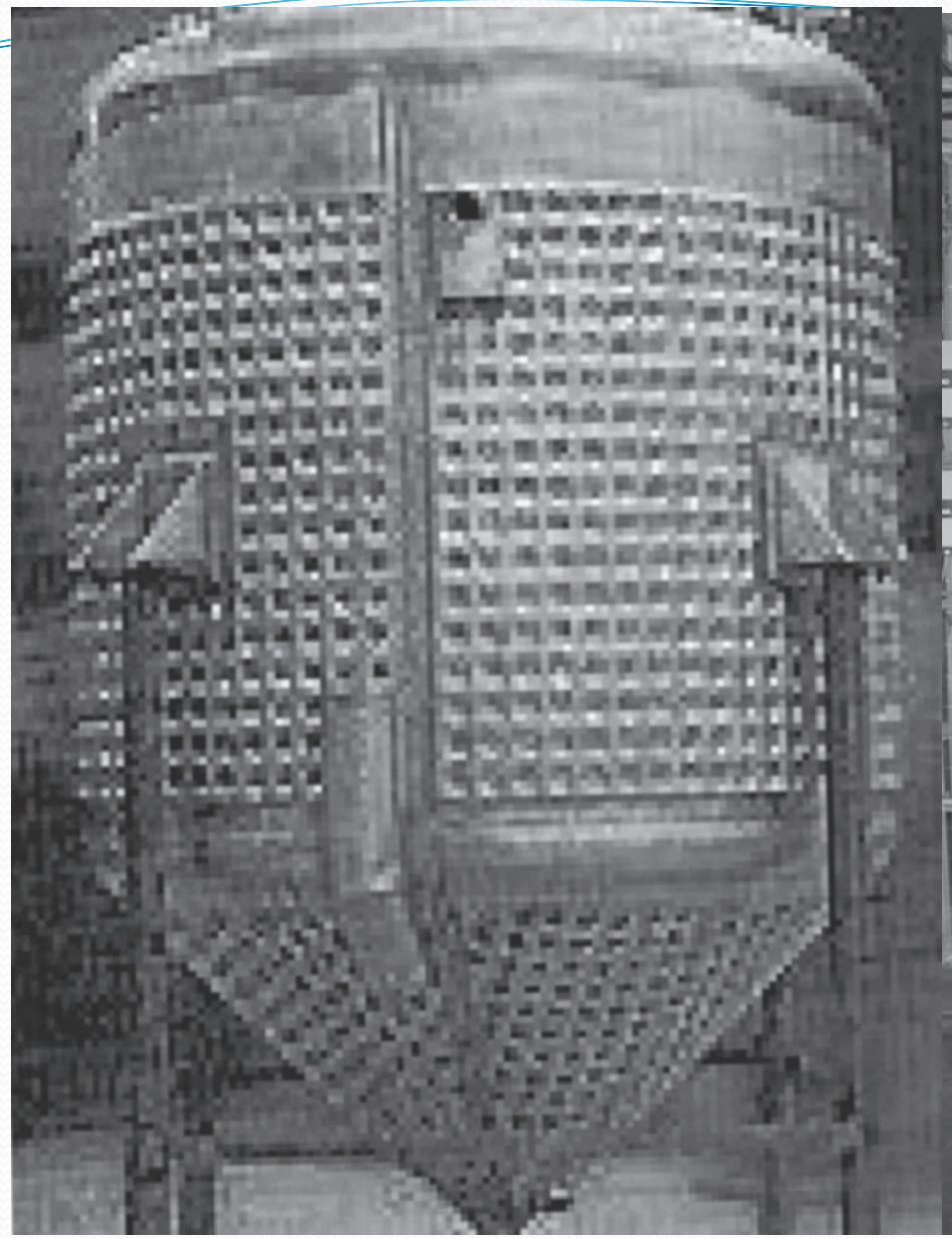
EQUIPMENT REQUIREMENTS

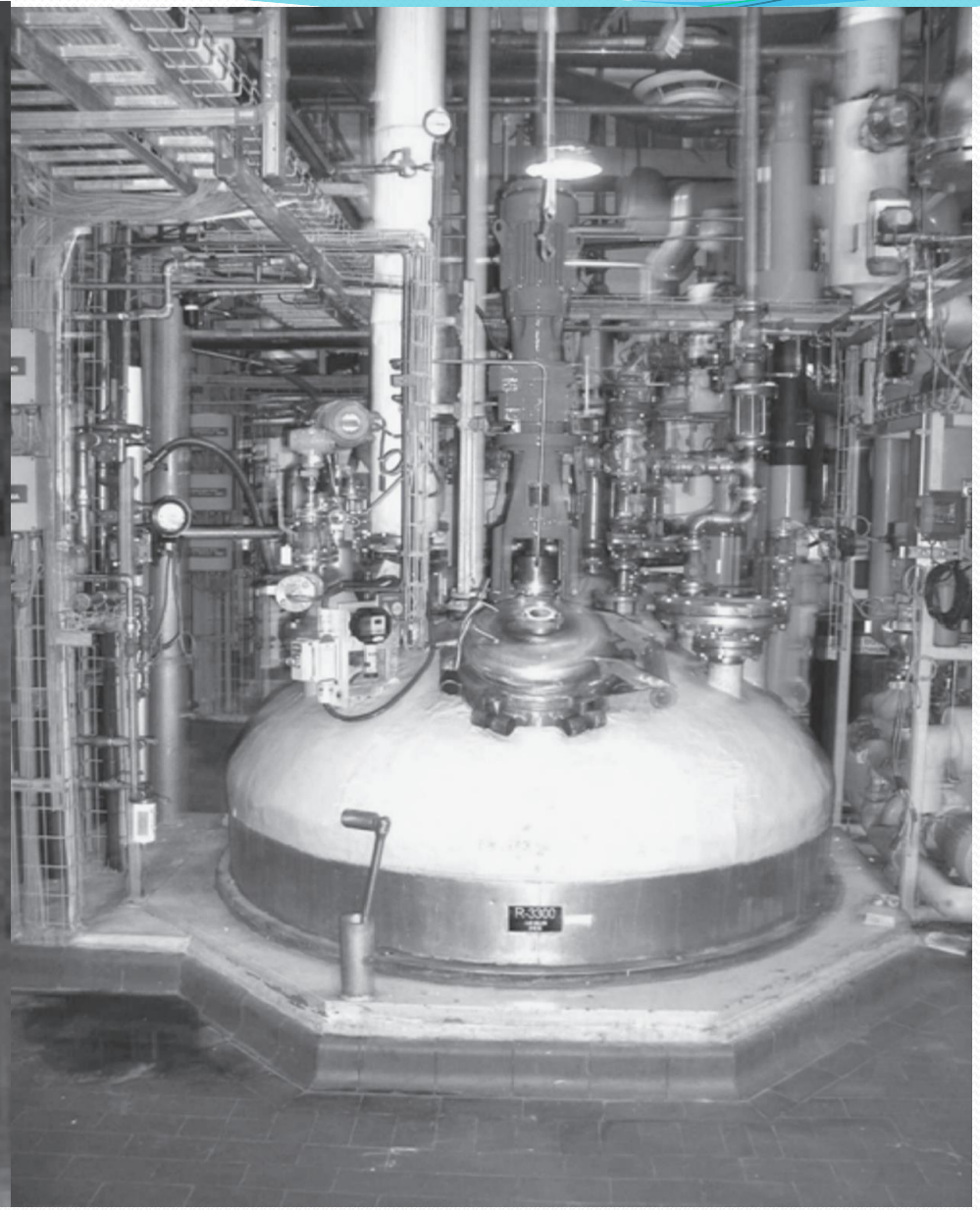
- Dryer: A dryer reduces the solvent or water content of an API before further processing or packaging.

- Mill/Sifter : reduces the API product to the necessary particle size and segregates out any oversized API product prior to bulk packaging.

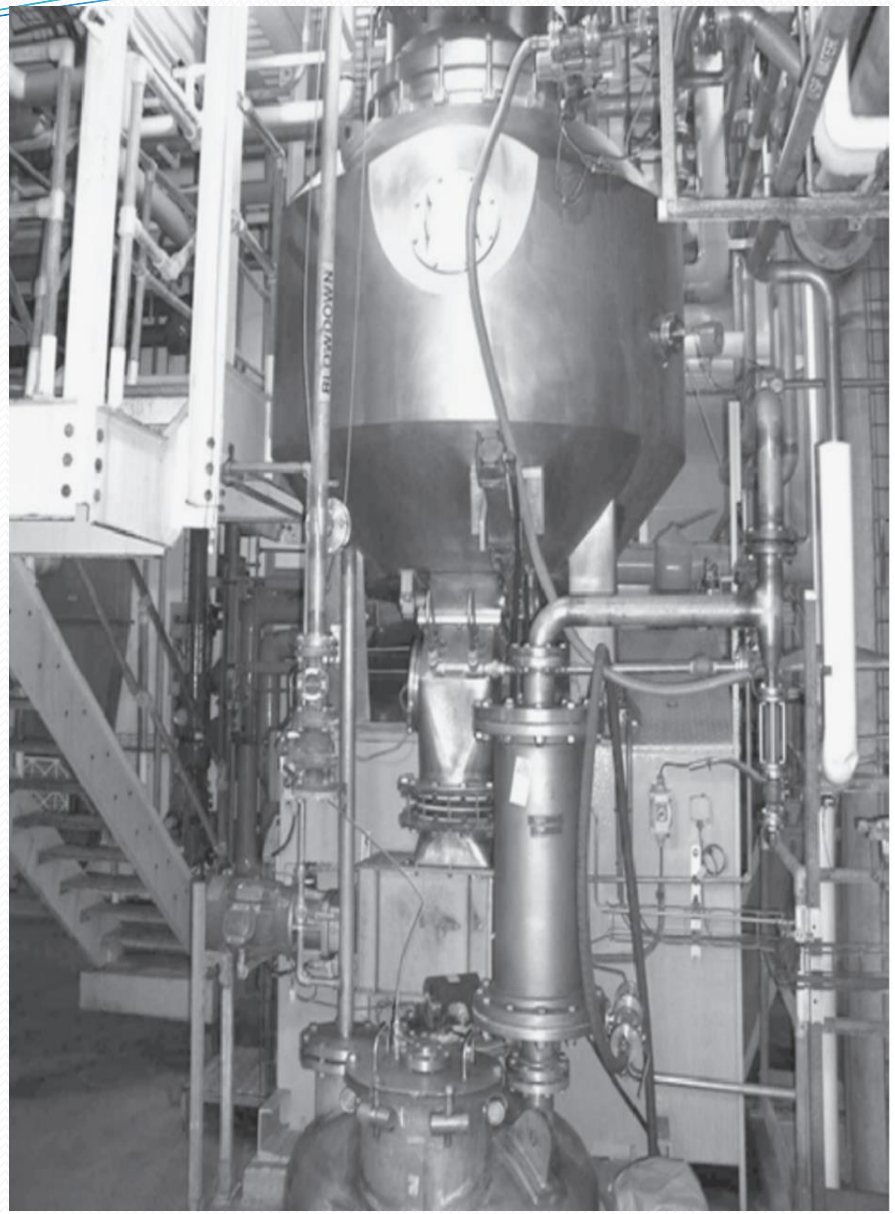
- Cleaning Equipment/CIP Systems: Cleaning equipment consists of devices that effect the cleaning of the components of an API manufacturing process train.

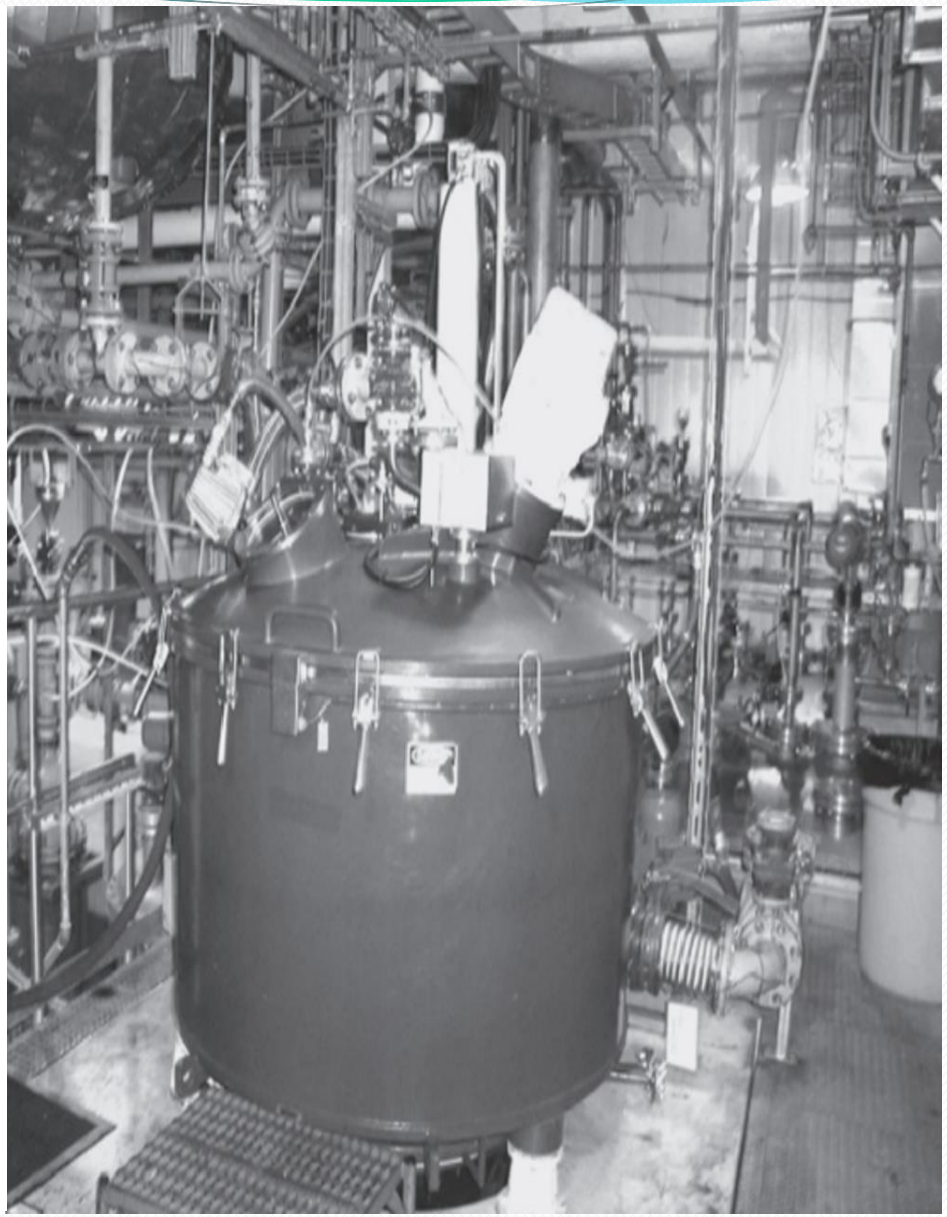
DESIGN OF API FACILITIES CONT....





DESIGN OF API FACILITIES CONT....





DESIGN OF API FACILITIES CONT....

DESIGN OF API FACILITIES CONT....

Process Configuration(s)

- The equipment that comprises the basic unit operations of an API manufacturing
- process must be connected together via piping systems and/or equipment movements in order to create an actual manufacturing process configuration.

DESIGN OF API FACILITIES CONT....

PROCESS HAZARDS/SAFETY SYSTEMS

- API manufacturing processes are inherently hazardous due to the use of flammable, corrosive, or toxic liquids; flammable, corrosive, or toxic gases; and combustible organic powders.
- Chemical reactions must be evaluated for the potential to get out of control or run away, and proper safety devices or systems must be evaluated.
- proper safety devices or systems must be evaluated.
- API process operations such as vessel charging or emptying, product or material transfer, etc. must be evaluated for safety risks
- The aforementioned safety risks and other safety risk are best identified by a team of experienced API plant personnel while performing a structured process hazard analysis such as a Hazards and Operability review (HAZOP)

DESIGN OF API FACILITIES CONT....

WASTE TREATMENT/ENVIRONMENTAL SYSTEMS

❖**Vent Gas Extraction and Treatment System**:

This system collects all of the contaminated gaseous discharges from an API plant and treats the gas stream so that the contaminants are not discharged into the atmosphere.

❖**Liquid Waste Collection and Treatment System**:

This system collects all of the hazardous or contaminated liquid discharges from an API plant and treats them so that the contaminants are not discharged into the environment.

❖**Solid Waste Collection and Treatment:**

This system collects all of the hazardous or contaminated solid discharges from an API plant and treats or processes them so that the contaminants are not discharged into the environment .

DESIGN OF API FACILITIES CONT....

RISK ANALYSIS

- During all stages of the design of API manufacturing facilities, a risk analysis must be performed.
  This risk analysis must include evaluations in terms of the following items:
  Differences Between Manufacturing APIs and Other Materials Such as Excipients:
  The risks involved with the manufacture of a particular material will depend on what final drug product the material will be used in.

DESIGN OF API FACILITIES CONT....

RISK ANALYSIS

- **Conditions for Receipt, Storage, Handling and Processing of Starting Materials:**

Starting materials may be purchased from a supplier or produced in-house.
If purchased, then controls must be established in terms of storage, sampling, release testing, handling, and use of such materials.

- **Differences in Levels of Control for Starting Materials, Intermediates vs. Final API Product:**

As the process moves closer to the final API, the control requirements must be more stringent including the cleaning residues criteria and the documentation related to the process steps.

DESIGN OF API FACILITIES CONT....

LEVELS OF PROTECTION

- **Level I: General**: Normal housekeeping and maintenance.

- **Level II: Protected**: Various steps such as restricted personnel entry and use of gowning and foot covers are set to protect exposed intermediates and APIs.

- **Level III: Controlled**: Environmental control levels such as air particles are set and monitored.

DESIGN OF API FACILITIES CONT....

FACILITY REQUIREMENTS

❖ **Location and Size:**

- **The size of the building must allow adequate space for the proper operations to be performed including receiving, storage, manufacturing,cleaning,..etc.**
- **The location must consider aspects such as environmental conditions; water, natural gas, electricity, ..etc.**

❖ **Building Materials and Features:**

The materials used for construction must be appropriate for the product/process being considered.

Materials should also be adequate to address safety

❖ **Electrical Systems and Classification(s)**

DESIGN OF API FACILITIES CONT....

PROCESS UTILITIES

- Any substance (liquid or gas) that comes in contact with the API, intermediates, or the equipment/facility product contact surfaces must comply with the required company defined specifications.

This includes:

1. **Direct Contact Steam Systems and Boilers: These systems interact directly with the product raw materials or with equipment that comes in contact with raw materials.**

2. **Compressed Gases: These systems consist of process raw material gases such as hydrogen, chlorine, ammonia, etc.**

3. **Water Generating and Distribution Systems: These must comply with USP Purified Water standards if used on a product intended for parenteral product.**

4. **Cleaning Solutions/Agents: These agents must be suitable for the cleaning applied.**

DESIGN OF API FACILITIES CONT....

LIGHTING AND VENTILATION

- Lighting must be adequate to facilitate proper execution of manufacturing, maintenance, cleaning, and testing procedures.

ENVIRONMENTAL CONDITIONS

- Environmental conditions in the areas should be kept so as not to adversely affect the products or materials within the area.

DESIGN OF API FACILITIES CONT....

LAYOUT

A) **Equipment Type and Placement:**

Equipment must be designed and/or purchased as required by the processing steps.

The facility design should provide sufficient space as needed for the type and size of the equipment and appurtences required for such operations.

There must be sufficient space surrounding the equipment to allow proper access for cleaning, maintinace and other process related operations associated with the system.

DESIGN OF API FACILITIES CONT....

LAYOUT

B) Areas:

1. Production/Manufacturing: The production area will generally utilize the largest portion of the facility.

2. Storage: Adequate space must be provided for storage of material. Materials include received components/ ingredients, intermediates, APIs, or any other related item purchased for the manufacturing process

3. Sampling Areas: These areas could require environmental controls and safety equipment availability when applicable for those raw materials and other chemicals, which could be hazardous to the employee.....

4. Packaging and Labeling: These areas must be segregated to avoid cross-contamination and possibilities of a mix-up of different materials.

DESIGN OF API FACILITIES CONT....

5. Laboratories: Normally will be segregated from the manufacturing areas.In the case of in-process testing, these are allowed to be close to or inside manufacturing areas.

6. Locker and Restroom Facilities: Locker rooms and restroom facilities should be physically separated from the laboratory and processing areas by a room, corridor, or other intermediate space.

7.Gowning Areas: Gowning areas should be used when exposure to the product or m aterials could put personnel at risk and when it is necessary to prevent product contamination.

DESIGN OF API FACILITIES CONT....

FLOW OF MATERIALS AND PERSONNEL IN THE FACILITY

1. **Material Flows:** Material flows should be designed to provide easy movement of materials yet prevent product mix-ups, cross-contamination and contamination from the environment.

2. **Personnel Flows:** The design and equipment layout should allow adequate room for personnel access for routine and non-routine maintenance. The layout must also allow for sufficient room for personnel flows in compliance with the applicable building codes.

CLOSED VS. OPEN EQUIPMENT

Closed equipment is preferred to minimize the probability of contamination.

If open equipment is used, the facility must be designed to control the sources of possible contamination so that the product is protected.

Design Implications in Terms of Performance and Compliance

DESIGN OF API FACILITIES CONT....

1. **Quality Implications:**
   Proper design of an API facility can mean less opportunity for errors and quality concerns.

2. **Safety:**
   Safety is a matter of the highest priority in the design of a facility.

3. **Waste Disposal/EPA Issues: Waste disposal is a major area of concern in API facility design.**

4. **Flexibility:**
   The design of an API facility should incorporate elements of flexibility commensurate with its intended processing needs

DESIGN OF API FACILITIES CONT....

5. Standardization:

The design of an API facility or process improvement should seek to provide stan□dardized equipment, instrumentation, electrical system, etc.

6. Expansion and Bottleneck Concerns:

The design should take into consideration potential bottleneck concerns.

PROJECT MANAGEMENT ISSUES

DESIGN OF API FACILITIES CONT....

- **Project Approach**: An API manufacturing company has a variety of options available for implementing a new facility project or a plant renovation project.

- **Project Scheduling**: Milestones It is critical to prepare a project schedule for the definition, design, construction, start-up, commissioning, and validation of the facility.

- **Resources Allocation**: It is imperative to involve all appropriate functions during the entire design/ construction process, especially the Quality and Validation departments.
  Resources must be identified and committed for these activities

DESIGN OF API FACILITIES CONT....

- **Good Engineering Practices (GEPs) Throughout the Project:** **The application of the GEPs will support the overall GMP level of the design, construction, and start-up procedures and documentation so that the quality and validation functions will have a higher probability of success during the actual review of the design and qualification of the facility.**

  The application of GEPs recognizes that all systems in the facility routinely undergo some form of commissioning.

- Compliance and Validation Concepts: From Project Definition Through Design, Construction, Start-Up, and Commissioning:

- **Project Documentation:** **Any project related to an FDA-regulated facility of process requires a substantial amount of documentation.**

DESIGN OF API FACILITIES CONT....

TRENDS AND FUTURE DEVELOPMENT

1. **Biotechnology:** Vaccines Manufacturing, Virus, and DNA Removal Facilities.

2. **R&D and Clinical Material Manufacturing**: Facility and Equipment Requirements for Validation and Regulatory Compliance.

3. **Further Controls to Eliminate Cross Contamination**: Physical Barriers Between Equipment/Processes.

4. **Process Analytical Technologies**

Thank you